Cancer Council Australia

Clinical practice guidelines for the treatment and management of endometrial cancer

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Guidelines commissioned by

1 Clinical practice guidelines for the treatment and management of endometrial cancer

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Published: 2012

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1 Foreword

1.1 Foreword

Endometrial cancer is the most common invasive gynaecological cancer in Australia and specifically refers to cancer that arises from the lining of the uterus (called the endometrium). It affects approximately 1 in 69 Australian women before the age of 75 years. In 2010, about 2100 women were expected to be diagnosed with endometrial cancer. This means that across Australia in 2010, on average, six females were diagnosed with endometrial cancer each day.[1]

The incidence of endometrial cancer is increasing in Australia, due in part to an ageing population and an increasing prevalence of obesity (a known risk factor for the disease). Other risk factors for this cancer include history of endometrial hyperplasia, history of polycystic ovary syndrome, nulliparity, exposure to unopposed oestrogen, strong family history of endometrial or colon cancer (Lynch syndrome), and tamoxifen therapy.

Once the histological diagnosis of endometrial cancer is confirmed then the patient is offered treatment that in most cases is an operation to remove the uterus, fallopian tubes and ovaries. In some circumstances it may be appropriate to remove lymph nodes from the pelvic and aortic areas.

Cancer Australia's National Gynaecological Cancers Service Delivery and Resource Framework (2011), developed in partnership with the Royal Australian and New Zealand College of Obstetricians and Gynaecologists, recommends that 'all women with a suspected (i.e. with symptoms indicative of a high risk of cancer) or actual gynaecological cancer have access to a comprehensive multidisciplinary team led by a gynaecological oncologist to provide high-quality management based on the best available evidence and tailored to women's needs to achieve the best outcome for each woman.[2]

The following guidelines to clinical practice relate to **apparent** early stage endometrial cancer at the time of diagnosis, that may have low or high risk features. Since adjuvant treatment is most commonly recommended when disease is found on final pathology to be more advanced than initially thought, a decision was made early on to include more advanced stage disease in the adjuvant treatment chapters so the controversial issues of adjuvant radiotherapy and chemotherapy could be addressed.

There is a lack of strong evidence for many of the treatment options available to women with this cancer and it is hoped that this publication will assist doctors and their patients in making informed choices about management options.

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1.1.1 References

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2 Summary of recommendations

2.1 Summary of recommendations

2.2 Endometrial cancer

2.2.1 Multidisciplinary care

2.2.2 Is there benefit for multidisciplinary care of women with low and high-risk apparent early stage endometrial cancer?

Recommendation	Grade
All patients with endometrial cancer should have the benefit of multidisciplinary team management, which includes review of pathology and relevant imaging, and	**C**

Recommendation	Grade
presentation of their case at a multidisciplinary team conference.	

Point(s)
It is recommended that all patients should have access to subspecialist (gynaecological oncologist) care in the management of their gynaecological cancer.
Patients may benefit from multidisciplinary team approach at a number of points during their care, including: changes in major treatment modality (surgery, radiotherapy, chemotherapy) post-treatment survivorship care and decisions regarding palliative care.

2.2.3 Is there benefit for multidisciplinary care of women with low and high-risk apparent early stage endometrial cancer?

Recommendation	Grade
All patients with endometrial cancer should have the benefit of multidisciplinary team management, which includes review of pathology and relevant imaging, and presentation of their case at a multidisciplinary team conference.	**C**

Point(s)
It is recommended that all patients should have access to subspecialist (gynaecological oncologist) care in the management of their gynaecological cancer.
Patients may benefit from multidisciplinary team approach at a number of points during their care, including: changes in major treatment modality (surgery, radiotherapy, chemotherapy) post-treatment survivorship care and decisions regarding palliative care.

2.2.4 Pre-operative investigations

2.2.5 What is the role of preoperative imaging for low and high risk apparent early stage endometrial cancer?

Recommendation	Grade
Routine 'predictive' preoperative imaging with abdomino-pelvic CT scan is NOT indicated in clinically early stage endometrial cancer where the tumour appears to be confined to the uterine body and is of low grade (1-2) endometrioid histological type.	**C**
Preoperative abdomino-pelvic CT scan is indicated in patients who have symptoms, signs or blood tests suggestive of metastatic disease or high-grade or high-risk histologic type of endometrial carcinoma.	**C**
Preoperative MRI may be helpful when there is clinical suspicion of cervical involvement as confirmation will guide surgical management.	**B**
Preoperative 'predictive' imaging may be useful in patients who are not suited to full surgical staging and may assist in 'staging' and planning management.	**C**
Preoperative MRI may assist in the assessment of patients wishing to retain fertility.	**D**

Point(s)
In Australia and elsewhere there is a trend toward a laparoscopic surgical approach to endometrial cancer, thus reducing the opportunity for full visual exploration and palpation of the peritoneal cavity and aortic and pelvic retroperitoneal nodes (*see section on Hysterectomy*). In patients in whom a laparoscopic approach is planned, it may be useful to perform a CT scan of abdomen and pelvis to exclude gross pelvic organ abnormality, or retroperitoneal nodal enlargement.

2.2.6 Is there a benefit to a histopathological review of currettings or biopsy prior to treatment in low and high risk apparent early stage endometrial cancer?

Recommendation	Grade
Pre-operative review of uterine curettings or endometrial biopsies by a specialist gynaecological pathologist is recommended to assist in the accurate tailoring of treatment.	**C**

2.2.7 Surgery

2.2.8 What is the evidence based surgical approach for hysterectomy in low and high risk apparent early stage endometrial cancer?

Recommendation	Grade
Laparoscopic approach to the management of endometrial cancer can be considered by appropriately trained surgeons, as it has been found to be feasible and surgically safe with reduced post-operative complications and length of stay. Data on the oncological safety are still awaited.	**B**

2.2.9 What is the evidence based surgical approach for bilateral salpingo–oophorectomy in premenopausal women with low and high risk apparent early stage endometrial cancer?

Recommendation	Grade
Consideration should be given to retaining ovaries in young women less than 45 years of age with endometrial cancer whose ovaries appear normal at operation and have no adverse risk factors.	**C**
Patients with Lynch Syndrome should be counselled that their ovaries should be removed at the time of hysterectomy given the high lifetime risk of developing ovarian cancer.	**C**

2.2.10 What is the evidence based surgical approach for lymphadenectomy in low and high risk apparent early stage endometrial cancer?

Recommendation	Grade
A simple hysterectomy and bilateral salpingo-oophorectomy may be considered optimal surgery for patients with apparent stage 1A Grade 1 or Grade 2 endometrioid adenocarcinoma of the uterus.	**B**
Pelvic lymphadenectomy may be carried out in surgically fit patients with grade 3 endometrioid adenocarcinoma, deeply invasive (more than 50% myoinvasion) grade 1 and grade 2 tumours, cervical involvement, palpably enlarged nodes, or	**B**

Recommendation	Grade
endometrioid tumours greater than 2cm, for accurate staging and appropriate planning and tailoring of adjuvant therapy.	
A para-aortic lymphadenectomy may be considered in selected groups of patients with positive pelvic nodes, palpably enlarged para-aortic nodes, tumour involvement of the cervix, or adnexal disease for accurate staging and appropriate planning and tailoring of adjuvant therapy.	**C**

Point(s)
While lymphadenectomy is part of the current FIGO 2009 surgical staging for endometrial cancer, it is important for clinicians to consider the benefits, limitations and morbidity of the procedure in the absence of compelling evidence for any survival advantage related to full surgical staging. This is of particular importance in patients who are at lower risk of nodal metastasis.

2.2.11 What is the role of intra-operative assessment of the uterus in low and high risk apparent early stage endometrial cancer?

Recommendation	Grade
Caution should be exercised in relying on intra-operative assessment of depth of invasion, involvement of cervix and histological grade as a means to determine extent of surgical staging	**C**
Patients with high grade, histologically aggressive or large tumours are unlikely to benefit from intra-operative assessment.	**D**

Point(s)
Intra-operative assessment may be used to identify those patients with (apparent) low-stage and low-grade endometrioid adenocarcinomas who have adverse prognostic features identified only at operation.

2.2.12 Adjuvant therapy

2.2.13 After hysterectomy, what is the role of radiotherapy (external beam, brachytherapy) in the management of early stage high risk endometrial cancer?

Recommendation	Grade
Adjuvant radiation can be offered to those stage 1 patients with risk factors in order to improve local control.	**B**
In selected at-risk patients, use of VBT alone over pelvic EBRT can be considered to reduce toxicity.	**B**
It is reasonable to follow the PORTEC-2 dosing guidelines for adjuvant brachytherapy. The equivalent VBT dose should be limited to below 60 Gy/2 Gy per fraction.	**D**
The addition of EBRT to VBT in higher risk patients with early stage disease can be considered in order to improve local control. For combined VBT and pelvic EBRT, PORTEC-3 Guidelines can be used to guide radiotherapy dosing.	**C**
Patients with apparent stage 2 tumours, combined use of EBRT and VBT is recommended. In those patients with stage 2 (full surgical staging), VBT alone can be considered.	**D**

2.2.14 After hysterectomy, what is the role of chemotherapy (concurrent /concomitant, sequential, sandwich, chemoradiation) in the management of early stage high risk endometrial cancer?

Recommendation	Grade
Patients with completely resected stage I-III high-risk disease can be counselled that the use of adjuvant chemotherapy in addition to radiotherapy may improve progression-free survival rates compared to the use of adjuvant radiotherapy alone, particularly if their histology is endometrioid. There is no evidence that overall survival is improved. These patients should be encouraged to consider enrolment into clinical trials addressing this question.	**B**
Patients with uterine papillary serous cancer (UPSC) or clear cell (CC) uterine cancer should be counselled that there is only low level evidence that adjuvant chemotherapy may have any impact on survival.	**D**

Recommendation	Grade
Patients treated with sequential adjuvant chemotherapy and radiotherapy may receive the full course of chemotherapy either before or after radiotherapy, or given as part of a sandwich regimen. Acceptable chemotherapy regimens include cisplatin and doxorubicin or carboplatin and paclitaxel.	**C**
The use of chemotherapy should be considered for patients with stage IV disease or those with stage III disease plus residual disease at the completion of surgery. Pelvic radiotherapy should also be considered to reduce the risk of pelvic relapse, except perhaps in patients with widespread distant disease.	**B**

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2.1 Multidisciplinary care

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1 Is there benefit for multidisciplinary care of women with low and high-risk apparent early stage endometrial cancer?
- 1.1 The multidisciplinary team
- 1.2 Multidisciplinary care and clinical outcomes
- 1.3 Multidisciplinary care and psychosocial outcomes
- 1.4 Other benefits of multidisciplinary care

2 Evidence summary and recommendations
3 References
4 Supporting material

2.1.1 Is there benefit for multidisciplinary care of women with low and high-risk apparent early stage endometrial cancer?

Multidisciplinary care (MDC) can be defined as the coordinated involvement of clinical and allied specialists in the management of a particular patient.[1][2] The aims of MDC[3] are to:

- ensure that all patients receive timely treatment from appropriate professionals
- ensure that all relevant input from different specialities is considered in formulating a treatment plan
- ensure that all clinicians have complete information on the treatment plan, potential problems and prognosis

- ensure continuity of care
- ensure that patients get adequate information and support
- facilitate communication between primary, secondary and tertiary care providers
- audit and research clinical data
- monitor adherence to clinical guidelines

Practice point

It is recommended that all patients should have access to subspecialist (gynaecological oncologist) care in the management of their gynaecological cancer.

2.1.1.1 The multidisciplinary team

Multidisciplinary team (MDT) meetings may include input from gynaecological oncologists, medical and radiation oncologists, gynaecological pathologists, palliative care specialists, clinical geneticists, radiologists, trainee medical specialists, nursing and social work personnel, psychologists and research scientists to ensure all aspects of a woman's care, both physical and psychological, are considered.

Multidisciplinary case conference decisions should be carefully documented and communicated to all personnel involved in the woman’s care. The woman’s involvement in decisions is usually via the primary treating clinician, often a gynaecological oncologist. The treatment plan should always consider individual patient circumstances and wishes.

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2.1.1.2 Multidisciplinary care and clinical outcomes

In the post-operative setting, there may be several options for further treatment available to patients. A multidisciplinary care approach ensures that all suitable options are considered to support best patient outcomes.

No randomised clinical trials have been undertaken to compare clinical outcomes for oncology patients managed by MDTs versus management by individual clinicians[1][4][5] and there are no studies related specifically to endometrial cancer. Two studies from the UK have shown implementation of MDT recommendations in gynaecological oncology and upper GIT and colorectal cancers varies, with between 7% and 15% of recommendations not being followed.[4][5] Similarly, a prospective study of gynaecological cancer cases in the US noted that 84% of recommendations were followed.[6] The authors concluded that the benefit to clinical outcome was actual rather than potential as most recommendations were followed. A retrospective study of 533 cases of ovarian cancer provided evidence that improved survival was associated with management by a MDT.[7] Studies of other tumour sites have shown that MDT management can result in positive patient outcomes, in terms of diagnosis, increase in the proportion of patients staged, treatment planning, survival and patient satisfaction.[4][5][8]

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2.1.1.3 Multidisciplinary care and psychosocial outcomes

The psychosocial care of a patient begins from the time of initial diagnosis, through treatment, recovery and survival and involves all members of the multidisciplinary team, as well as the patient's GP, family, friends and carers. Psychosocial care covers physical, emotional, social, and psychological issues, such as self concept, body image and sexuality, as well as interpersonal difficulties, anxiety and fear.[9]

Treatment for endometrial cancer can lead to a number of changes, which can affect a woman's sexuality. Women and their partners require information and education about the effect the cancer and its treatment has on sexual function. A discussion about these aspects of the patient's care needs to be addressed by the health professionals.[10]

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2.1.1.4 Other benefits of multidisciplinary care

Studies of MDC have also shown benefits for patients other than clinical outcomes.[3][4] They include:

- Faster and more coordinated treatment with agreed treatment plans
- Improved care through best practice and adoption of evidence based guidelines
- Improved patient satisfaction with treatment
- More consistent information to patient
- Entry of eligible patients into trials of new therapies
- Educational opportunities
- Mutually supportive environment and reassurance from corporate decision making especially in complex cases
- Improved well being of members
- Improved communication between members

A UK survey, conducted between 2000-2004, showed increased patient satisfaction in breast, colorectal and lung cancer care, where MDT is more established.[5] Other reported benefits include improved professional performance (clinically appropriate care) through enhanced clinical expertise and improved coordination of care, resulting in positive effects on patient outcomes.[8]

Practice point
Patients may benefit from multidisciplinary team approach at a number of points during their care, including: changes in major treatment modality (surgery, radiotherapy, chemotherapy) post-treatment survivorship care and decisions regarding palliative care.

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2.1.2 Evidence summary and recommendations

Evidence summary	Level	References
Multidisciplinary care has been shown to improve care in accordance with evidence-based practice and to impact on treatment and management decisions.	III-3, IV	[4], [5], [6], [8], [11], [12]

Evidence-based recommendation	Grade
All patients with endometrial cancer should have the benefit of multidisciplinary team management, which includes review of pathology and relevant imaging, and presentation of their case at a multidisciplinary team conference.	**C**

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2.1.3 References

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2.1.4 Supporting material

- Initital literature search: Multidisciplinary team management

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2.2 Preoperative imaging

Contents

1 What is the role of preoperative imaging for low and high-risk apparent early stage endometrial cancer?
- 1.1 Transvaginal Ultrasound (TVS)
- 1.2 Computed tomography (CT)
- 1.3 Magnetic Resonance Imaging (MRI)
- 1.4 Positron Emission Tomography (PET)
- 1.5 Chest X Ray
- 1.6 Is there a role for preoperative imaging in endometrial carcinoma?

2 Evidence summary and recommendations
3 References
4 Supporting material

2.2.1 What is the role of preoperative imaging for low and high-risk apparent early stage endometrial cancer?

The use of some imaging techniques prior to definitive surgical treatment is routine in many gynaecological cancer treatment centres, but the evidence for this practice is unclear. If pretreatment imaging is to be of any value then it should influence patient management, such that the findings are used to determine the appropriateness, type and extent of planned surgery or treatment.

In Australia the possible indications for imaging in this situation are three-fold:

1. To exclude metastatic disease in the pelvis (adnexae or pelvic lymph nodes) or distant sites (lung, liver, omentum, peritoneal cavity or aortic nodes) in whom surgical treatment is planned.
2. To ‘stage’ tumours in women who are unsuited to full surgical staging by reason of morbid obesity and/or other medical co-morbidities.
3. To triage women who will most likely benefit from full surgical staging/lymphadenectomy by predicting the presence of locally advanced disease (deep myometrial invasion and/or cervical stromal involvement) as a surrogate for increased likelihood of pelvic/aortic node metastasis.

In Australia, recommended best practice for women with endometrial cancer is that they be managed by a gynaecological oncologist who will incorporate full surgical staging into the planned treatment where appropriate, thus minimising the value of predictive pre-operative imaging. Preoperative imaging may be appropriate for women who live in rural areas remote from subspecialist treatment centres who could potentially be treated by a local community gynaecologist without the need for full surgical staging.

The majority of women diagnosed with endometrioid adenocarcinoma of endometrium (EAC) will have a small uterus with grade 1-2 histology and will be at low risk of metastatic disease in the pelvis and elsewhere. The yield from a ‘metastatic imaging work up’ will be low in terms of discovering ‘radiologically apparent’ and clinically unsuspected spread of the disease.

The following imaging techniques can be considered:

1. Transvaginal Ultrasound (TVS)
2. Computed Tomography (CT)
3. Magnetic Resonance Imaging (MRI)
4. Positron Emission Tomography (PET)
5. Chest X Ray

2.2.1.1 Transvaginal Ultrasound (TVS)

Many women who have been diagnosed with endometrial cancer will have already had a transvaginal ultrasound as part of their diagnostic investigations, providing valuable information regarding the size of the uterus and the presence or absence of adnexal masses.

TVS is reasonably accurate (70-90% PPV) in the prediction of deep myometrial invasion and is inexpensive in comparison to CT and MRI.[1][2][3] Van Doorn considered TVS to be only moderately reliable in the prediction of deep myometrial invasion, but when combined with patient age and degree of tumour differentiation in the curettings it was possible to preoperatively select women at high risk of lymph node metastases with sufficient reliability.[4] Use in the Australian setting is unlikely to alter management decisions.

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2.2.1.2 Computed tomography (CT)

Several retrospective studies have suggested that pelvic and abdominal CT scanning has limited utility in the preoperative assessment of women with endometrial carcinoma.[5][6][7][8] CT showed poor prediction of nodal disease and depth of myometrial invasion though it was suggested it could have some utility in high-risk histologic types such as clear cell and serous papillary.[5][6]

In the largest and most recent series, Bansal reviewed the records of 762 women with uterine malignancies between 1990-2006.[7] Abdomino-pelvic CT scans were performed preoperatively in 250 women (32 sarcoma and 218 with carcinoma) and CT findings were correlated with intraoperative and histopathologic data. The analysis focused on extranodal metastatic disease and any other incidental findings, and their capacity to alter the planned management. Extra nodal disease was found in 22 (9%) of women (adnexa 10, omentum 4, bowel 3, ascites 1) but patient management was altered in only seven (3%). Of these seven women, four had grade 3 EAC, one had a sarcoma and the other two had grade 1 EAC. Incidental findings were noted in 43 (17%) and management altered in only seven (3%) of these women in whom the findings were considered important, namely renal mass in five, severe diverticular disease requiring resection in one and a retroperitoneal mass with hydronephrosis due to squamous carcinoma in one patient. Further analysis based on preoperative histologic diagnosis showed that CT findings were more likely to alter management (10.7%) in women with high-risk serous papillary and clear cell histologic subtypes.

They concluded that routine CT scanning of women with EAC is costly, of limited value and rarely alters treatment, but may have some utility in women with high-risk histology.[7]

(It should be noted that in the USA, where this study was done, it is recommended that full surgical staging be carried out on all women and, therefore, the predictive role of imaging is of less importance.)

However, in some situations the addition of a CT scan of thorax, abdomen and pelvis may be useful in defining or excluding distant metastases or local extension of the disease to the adnexae or pelvic/aortic lymph nodes. Such circumstances include:

1. Symptoms (cough, bloating, pain)
2. Physical signs (ascites, enlarged liver, upper abdominal mass, adnexal mass, cervical lesion)
3. Abnormal biochemical or haematological investigations (liver function tests, CA125 etc)
4. High-risk histologies (clear cell, serous papillary) or high-grade (3) endometrioid carcinoma

Practice point

In Australia and elsewhere there is a trend toward a laparoscopic surgical approach to endometrial cancer, thus reducing the opportunity for full visual exploration and palpation of the peritoneal cavity and aortic and pelvic retroperitoneal nodes (*see section on Hysterectomy*). In patients in whom a laparoscopic approach is planned, it may be useful to perform a CT scan of abdomen and pelvis to exclude gross pelvic organ abnormality, or retroperitoneal nodal enlargement.

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2.2.1.3 Magnetic Resonance Imaging (MRI)

MRI has been shown to be an accurate tool for the measurement of the depth of myometrial invasion by endometrial carcinoma though an isointense junctional zone, polypoid tumours or presence of leiomyomas may lead to an underestimate of myometrial invasion.[9] This study showed 83.3% accuracy in differentiating deep from superficial invasion in 100 of 120 cases.[9]

In a comprehensive literature review of the conservative management of endometrial cancer in young women, Erkanli suggested that MRI may be of assistance specifically in assessing the absence of invasion.[10] In a recent Australian study, Cade reported on progestogen treatment options for early endometrial cancer and considered an MRI scan negative for myometrial invasion or extension to the cervix an essential prerequisite to conservative treatment.[11]

In contrast, Nakao has reported that although MRI is good at determining deep myometrial invasion it is not as accurate in assessing the absence of microscopic myometrial invasion.[12] This view is supported by an Australian study in which Cade questions whether radiological staging is sufficient for planning conservative treatment. This study compared MRI scans and final histopathological diagnoses of 111 patients with endometrioid adenocarcinoma over a six year period at a tertiary centre.[13] They reported that MRI had a high negative predictive value (NPV) for the presence of deep invasion (87% overall and 95% for grade 1 disease), but a poor NPV for the presence of any myometrial invasion, making it less reliable in predicting the absence of invasion. However, if the new revised 2008 FIGO staging system was used then stage 1A (no invasion or up to 50% invasion) was more accurately predicted using MRI, making it very useful if clinicians were to consider all patients with stage 1A disease to be eligible for conservative treatment when fertility was desired. This is not current standard practice and more research is needed in this area.

In a retrospective review of 182 women diagnosed with clinical stage 1 disease, Cho et al studied the accuracy of preoperative investigations. They found that MRI correctly differentiated stage 1a, Ib and 1c disease in 58.2% (150/182) of patients but that the sensitivity and specificity of MRI in detecting lymph node metastases was only 45% and 80.8% respectively. They concluded that the inaccuracy of MRI would lead to incorrect surgical treatment in a substantial number of patients and that full systematic lymphadenectomy was necessary to determine the stage of the disease and tailor subsequent adjuvant therapy.[14]

MRI has been shown to be accurate in the prediction of cervical stromal involvement with a positive predictive value of 89.8% in a study of 135 consecutive women.[15] This is important as it will allow for an informed decision regarding the type of hysterectomy to be performed: radical rather than simple.

Celik evaluated cervical involvement in endometrial cancer by comparing transvaginal sonography (TVS), MRI and intraoperative frozen section in 64 consecutive patients.[3] The accuracy rates of TVUS, MRI and frozen section were 90.6%, 92.2% and 95.5% respectively. Obviously frozen section does not allow for alteration of the type of hysterectomy to be offered but will suggest the need for lymphadenectomy in patients without other high-risk prognostic factors. MRI was noted to be more time consuming and expensive than TVUS but could be recommended in cases where the TVUS was of poor quality.[3] MRI was found to be more reliable than diagnostic fluid mini-hysteroscopy and TVS in predicting cervical involvement with a positive predictive value of 71%, a negative predictive value of 94% and an accuracy rate of 91%.[16]

A meta-analysis of radiologic staging in patients with endometrial cancer was reported by Kinkel.[17] There were insufficient studies of CT and TVS for meaningful meta-analysis in regard to cervical involvement, but MRI showed equal specificity and sensitivity of 92% for prediction of cervical involvement.

Most authors have suggested that gadolinium contrast enhanced MRI is better for prediction of deep myometrial invasion,[18][19] but others have found no difference between T2 weighted and contrast enhanced MRI.[20][21]

MRI may be used to assess the depth of myometrial invasion in order to predict women with deep invasion greater than 50% of myometrial thickness and this finding has utility as a surrogate for the likelihood of lymph node metastases and to determine appropriate surgical treatment.[9][17][18][19][20]

It should be noted that nearly all of the MRI literature relates to the old FIGO 1988 staging. There is only one report regarding the efficiency of MRI in FIGO 2009 staged cases compared with FIGO 1988 staging.[22] Ballester reported that MRI staging was more accurate using FIGO 2009 but only moderately better.[22] It is possible that as more work is reported using FIGO 2009, the role of routine MRI will be clearer but at present the evidence is lacking.

MRI may be used in subspecialist tertiary centres for the assessment of cervical stromal involvement and appropriate surgical planning.

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2.2.1.4 Positron Emission Tomography (PET)

The use of positron emission tomography using fluoro-2-deoxyglucose (FDG-PET) has been studied in the preoperative evaluation of endometrial cancer.[23][24][25] FDG-PET has a sensitivity of 83.3% in detecting extrauterine lesions (excluding retroperitoneal nodes) and was useful in providing additional information regarding lesions detected on CT/MRI that were of uncertain significance.[23] FDG-PET was not able to identify any lymph node metastasis less than 1cm in diameter, and therefore a negative finding is not a reason to omit retroperitoneal lymph node dissection.[23]

Park retrospectively compared the validity of MRI and PET/CT in the preoperative evaluation of 53 women with endometrial cancer.[24] There was no difference in the ability of MRI or CT/PET to detect lymph node metastases and it was concluded that PET/CT could not replace surgical staging, but because of its high negative predictive value in predicting lymph node and distant metastases, it could be helpful in the assessment of patients who are unsuited for full surgical staging.[24]

Signorelli prospectively studied FDG-PET/CT in 37 fully surgically staged women confirming the results of other authors and the limitation in detecting nodal lesions of 5mm or less, probably related to the limited spatial resolution of PET/CT scanners used in the study.[25] They noted an accuracy of 94.4% in detecting nodal disease and concluded that the high NPV of 93.1% may be useful in selecting patients who may benefit from lymphadenectomy.[25]

PET or PET/CT may be used in subspecialist tertiary centres for the assessment of some patients and appropriate surgical planning. It is more commonly used post operatively, when the surgico-pathological findings show locally advanced disease or pelvic node involvement, in order to direct appropriate adjuvant therapy.

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2.2.1.5 Chest X Ray

Chest X Ray is part of the routine preoperative assessment of patients being considered for major surgery and may detect unexpected metastatic disease. While the yield is relatively low, it is cost effective, has low dose exposure and should remain a part of routine pre-operative assessment.

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2.2.1.6 Is there a role for preoperative imaging in endometrial carcinoma?

In Australia it is recommended that women with endometrial carcinoma are treated by gynaecological oncologists within specialist gynaecological oncology units. Patients have selective surgical staging based on tumour grade and histologic type and intraoperative assessment. Gynaecological oncologists have the facility to perform intraoperative uterine assessment and full surgical staging where indicated and consequently there is a reduced role for routine ‘predictive’ preoperative imaging.

If patients have symptoms, physical signs or abnormal blood tests suggestive of metastatic disease, then appropriate imaging, usually an abdomino-pelvic CT, is indicated to exclude pelvic or distant metastases. If there is a suspicion of cervical involvement then an MRI may be informative and guide surgical treatment.

For rural patients who are reluctant to travel to a gynaecological cancer centre for their treatment, and for whom the use of MRI to predict deep myometrial or cervical stromal involvement is not an option, Transvaginal scanning by an experienced practitioner or abdomino-pelvic CT may also be of assistance, as these investigations are more likely to be available in a community setting.

In women who are unsuited to full surgical staging by reason of morbid obesity or other medical co-morbidities, then MRI or FDG-PET/CT may be indicated to assist in ‘staging’ the patient. This will allow more accurate targeting of adjuvant or nonsurgical management

A Canadian population based study reviewed records of 12,522 women treated for uterine adenocarcinoma or sarcoma between 1995 and 2005.[8] A preoperative TVS was performed in 9145 (73%) women and 1148 (9.2%) had a CT and/or MRI.[8] Over the ten year period the use of CT had increased 4.5 fold and MRI use increased 10.6 fold. Significantly higher rates of CT/MRI use were seen in non-endometrioid high risk histology (33.5% versus 14.6%). Half of these tests were ordered by non-gynaecologists and the time from diagnosis to surgery was two weeks longer for women who had a CT/MRI. Given the questionable utility of preoperative CT/MRI in this disease, they recommended that guidelines be developed for the use of such imaging tests in uterine cancer.[8]

While the evidence for many of the imaging tests done pre-operatively is inconsistent and must be interpreted in the setting in which a patient is being managed, tests that will alter or help patient management should be considered.

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2.2.2 Evidence summary and recommendations

Evidence summary	Level	References
Abdomino-pelvic CT scan has limited utility in the preoperative assessment of women with endometrial carcinoma with poor prediction of nodal disease and depth of myometrial invasion.	III-2	[5], [6], [7], [8]

Evidence-based recommendation	Grade
Routine ‘predictive’ preoperative imaging with abdomino-pelvic CT scan is NOT indicated in clinically early stage endometrial cancer where the tumour appears to be confined to the uterine body and is of low grade (1-2) endometrioid histological type.	**C**

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Evidence summary	Level	References
Abdomino-pelvic CT scan may have some utility in discovering or excluding distant metastases or locally advanced pelvic disease particularly in high-risk histologic types or high-grade endometrioid adenocarcinoma of the endometrium.	III-2	[7], [8]

Evidence-based recommendation	Grade
Preoperative abdomino-pelvic CT scan is indicated in patients who have symptoms, signs or blood tests suggestive of metastatic disease or high-grade or high-risk histologic type of endometrial carcinoma.	**C**

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Evidence summary	Level	References
MRI is an accurate test for preoperative prediction of cervical involvement by endometrial carcinoma.	I, II	[15], [16], [17]

Evidence-based recommendation	Grade
Preoperative MRI may be helpful when there is clinical suspicion of cervical involvement as confirmation will guide surgical management.	**B**

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Evidence summary	Level	References
MRI is the most accurate method of preoperative prediction of depth of myometrial invasion by endometrial carcinoma.	I, II, III-1	[17], [18], [19], [20]
Preoperative tests based on tumour grade and MRI prediction of myometrial invasion are inaccurate in risk stratification for nodal metastases and fail to detect a small proportion of high-risk patients.	III-2	[14]
PET scan has a high negative predictive value for lymph node and distant metastases in endometrial carcinoma.	II, III-2	[23], [24], [25]

Evidence-based recommendation	Grade
Preoperative ‘predictive’ imaging may be useful in patients who are not suited to full surgical	

Evidence-based recommendation	Grade
staging and may assist in 'staging' and planning management.	**C**

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Evidence summary	Level	References
MRI is good at preoperative prediction of deep myometrial invasion but is less accurate at completely excluding superficial microscopic myometrial invasion.	III-2	[12]
MRI is the best available method of determining the likely absence of myometrial invasion in women desiring conservative management of endometrial carcinoma and wishing to retain fertility.	IV	[10]

Evidence-based recommendation	Grade
Preoperative MRI may assist in the assessment of patients wishing to retain fertility.	**D**

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2.2.4 Supporting material

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2.3 Pathological review

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1 Is there a benefit to a histopathological review of currettings or biopsy prior to treatment in low and high risk apparent early stage endometrial cancer?
1.1 Preoperative assessment
1.1.1 Review of endometrial biopsies or curettings
2 Evidence summary and recommendations
3 References
4 Supporting material

2.3.1 Is there a benefit to a histopathological review of currettings or biopsy prior to treatment in low and high risk apparent early stage endometrial cancer?

2.3.1.1 Preoperative assessment

2.3.1.1.1 Review of endometrial biopsies or curettings

The allocation of endometrial cancer to low and high risk is dependent on a number of features, only two of which are assessable pre-operatively, namely the histological type and grade. Histological review may change the preoperative diagnosis of the type and grade of tumour, from possibly low risk (grade 1-2 endometrioid tumours) to definitely high risk (grade 3 tumours, serous, clear cell carcinoma or to carcinosarcomas). Many gynaecological oncologists routinely review histopathological specimens from endometrial sampling with a gynaecological pathologist, prior to treatment. In many cases, the original diagnosis has been made in general pathology departments in regional or other metropolitan hospitals.

Only one retrospective study has studied the frequency of change in diagnosis after review of endometrial curettings and biopsy in detail.[1] Of 182 specimens, 16 (8.8%) were reclassified from malignant to premalignant or benign; in another 16 cases (8.8%), the histological type of tumour was changed significantly. Eleven of these 16 cases involved a change between endometrioid carcinoma and serous carcinoma, with another five cases (2.7%) reclassified from carcinocarcinoma to other sarcomas or carcinomas. The primary site of disease was changed from endometrium to cervix in three patients (1.6%) and vice versa in one patient. Overall, 23.6% showed major discrepancies. A study by Khalifa et al showed a reclassification of endometrial cancer histological type in 9.4%,[2] consistent with data from the study by Jaques.

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2.3.2 Evidence summary and recommendations

Evidence summary	Level	References
Pre-operative pathology review resulted in a change in histological type in 9%,	III-2	[1], [2]

Evidence summary	Level	References
downgrading of diagnosis to benign in 9%, change in differentiation (by 2 grades) in 1% and change in primary site in 2% of patients, resulting in significant changes in management.		

Evidence-based recommendation	Grade
Pre-operative review of uterine curettings or endometrial biopsies by a specialist gynaecological pathologist is recommended to assist in the accurate tailoring of treatment.	**C**

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2.3.3 References

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2.3.4 Supporting material

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2.4 Hysterectomy

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2.4.1 What is the evidence based surgical approach for hysterectomy in low and high risk apparent early stage endometrial cancer?

The standard management of patients with endometrial cancer is removal of the uterus, tubes and ovaries with pelvic and paraaortic lymphadenectomy, as necessary, for staging and management planning. This procedure has traditionally been performed by laparotomy. While there is no doubt about its efficacy, there have been concerns about the incidence of surgical morbidity and quality of life issues related to open hysterectomy through laparotomy, which has raised interest in minimally invasive techniques.

With the introduction of any new surgical technique, the feasibility, safety, and efficacy must be compared with the current standard surgical approach. Analysis of cost effectiveness and evaluation of impact on patient quality of life is also important. A number of retrospective analyses, single institution prospective studies and meta-analyses have been reported in the literature. However, these have generally involved small patient numbers, were subject to selection bias and offered short duration follow up only.[1][2][3][4][5][6][7][8]

Recently, the results of three large multi-institution randomised controlled trials (RCTs) have become available with information on feasibility, safety, benefits and impact on quality of life, when surgery for endometrial cancer is performed by laparoscopy compared with laparotomy.[9][10][11][12]

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2.4.1.1 Feasibility

2.4.1.1.1 Conversion rates

Since the introduction of laparoscopic hysterectomy more than 20 years ago, new technologies and increasing operator experience has led to a reduction in the rate of intraoperative conversion from a laparoscopic approach to laparotomy. This is reflected in the literature when reviewing conversion rates for laparoscopic procedures to laparotomy for endometrial cancer. Rates of conversion vary widely between different studies, likely due to varied experience between centres in laparoscopic surgery, and due to varied inclusion and exclusion criteria applied to patients enrolled in these studies.[13]

The US Gynaecologic Oncology Group (GOG) recently published an RCT comparing laparoscopy to laparotomy in 2616 patients with newly diagnosed FIGO Stage I to IV endometrial cancer (GOG Study LAP2).[10] The laparoscopic arm included patients undergoing laparoscopically assisted vaginal hysterectomy (LAVH), total laparoscopic hysterectomy (TLH), and rarely, robotic procedures. A conversion rate of 25% was reported. Common reasons cited for conversion were: the need to perform aortic node dissection irrespective of intra-operative findings, metastatic disease (unknown preoperatively), and risk factors such as (morbid) obesity resulting in poor exposure, and increasing age. Fifty-seven per cent of patients with a BMI > 40 kg/m2 required conversion, compared to only 17.5% of patients with a BMI <25 kg/m2. Despite this high conversion rate, a benefit was still seen in terms of lower rates of postoperative complications (grade 2 or greater), and shorter hospital stay.[10]

The Laparoscopic Approach to Carcinoma of the Endometrium (LACE) Trial is an RCT involving centres in Australia, New Zealand and Hong Kong. In contrast to the LAP2 study, this group reported a 2.4% conversion rate, which even included patients converted from the total abdominal hysterectomy (TAH) to the TLH group because of patient preference.[11] This conversion rate is extremely low when compared to other studies reporting rates between 4% and 10.8%.[1][3][5][9]

The low conversion rate seen in the LACE trial is likely to be due to several factors. There were strict eligibility criteria for both patients and surgeons. Only patients with stage I endometrial cancer, ECOG of <2, CT suggesting an absence of extra-uterine disease, uterine size <10 weeks, and who were medically fit were eligible. Lymph node dissection was not performed if the tumours were well or moderately differentiated and invaded into less than the inner half of the myometrium or if the patients were medically unfit. As a result of those criteria, only 52% of LACE patients had pelvic or paraaortic lymph node dissection. In addition, surgeons underwent a rigorous accreditation process to ensure procedural competence.

In 2010, Mourits et al. published a prospective randomised trial involving 283 patients in 21 centres in the Netherlands assessing safety of laparoscopic versus open hysterectomy in patients with stage I endometrial cancer or complex atypical hyperplasia.[9] All surgeons were experienced in laparoscopic surgery, and a conversion rate of 10.8% was recorded.

Conversion to laparotomy increases with co-morbidities (including morbid obesity) and increasing stage of disease.[10] Consideration of medical conditions such as severe cardiopulmonary disorders precluding steep Trendelenburg positioning in particular need to be considered when contemplating a laparoscopic approach.[14][15].

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2.4.1.1.2 Performance of pelvic lymph node dissection

While there is ongoing debate as to the role and extent of lymphadenectomy required in the management of endometrial cancer (*see section on Lymphadenectomy*),[16][17][18] a number of studies have confirmed that laparoscopic lymphadenectomy is feasible. In the GOG LAP 2 trial, paraaortic nodes were successfully retrieved in 94% of laparoscopic procedures, compared with 97% of procedures performed by laparotomy.[10] A number of RCTs comparing laparoscopy versus laparotomy did not detect any difference in number of nodes harvested, although the studies were not powered to detect a difference.[4][5][7][8][10][11]

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2.4.1.1.3 Operating time

Published studies show that laparoscopic surgery of endometrial cancer involves a longer operating time compared to laparotomy. This has been confirmed by RCTs to be statistically significant.[9][10][11] In general, the three RCT's showed that operating times for laparoscopic approach are 1.27 to 1.62 times longer than for laparotomy.

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2.4.1.2 Safety

2.4.1.2.1 Intra-operative adverse events

Laparoscopic management of endometrial cancer appears comparable to the open approach in regards to the incidence of intra-operative complications. Retrospective and single institution studies suggest less tissue trauma and blood loss compared to open procedures.[3][14] These findings have been confirmed in the recently performed RCTs.[9][10][11]

The Dutch Trial[9] found no significant difference in major intra-operative complication rates when comparing the laparoscopic to an open approach. However, TLH was associated with significantly less blood loss. No pelvic lymph node sampling was performed in this trial.[9] The LAP2 trial also reported no differences in intra-operative adverse event rates between the laparoscopic and open arms (p=0.106).[10] In the LACE trial was no difference in intra-operative adverse events between the laparoscopic and open arms.[11] 2.9% of patients sustained a vaginal injury in the TLH arm compared to none in the open arm.

2.4.1.2.2 Postoperative adverse events

A heterogeneous group of RCTs enrolling patients with different eligibility criteria have shown a significant advantage of laparoscopy over laparotomy in regards to the incidence of post-operative surgical adverse events. [4][5][7][8][9][10][11]

While there was no significant difference in post-operative complication rates reported by Mourits et al., half as many serious adverse events were seen in the TLH group compared to the TAH group in the LACE study.[9][11] In both the LACE and LAP2 trials, post-operative adverse events were classified using the Common Toxicity Criteria for Adverse Events (CTCAE) (VER3).[19]

The LAP2 study found CTCAE equal to or greater than grade 2 (moderate to severe adverse events) were more common in the open group compared to laparoscopic group (21% versus 14%, $p<0.004$).[12] This was due mainly to an increase in post operative ileus and arrhythmia in the laparotomy group. An increase in post operative adverse events was also seen in the LACE trial (53.8% versus 42.8%, $p=0.004$). In LACE, the difference was mainly due a large difference in the wound infection/dehiscence rate (30.9% in the open group versus 8% on the laparoscopic group).

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2.4.1.3 Quality of life (QOL)

An intention to treat analysis of patients in the LAP2 study found patients in the TLH arm had significantly better QOL, fewer physical symptoms, less pain and pain related interference with functioning, better physical functioning and emotional state, earlier resumption of normal activities, earlier return to work, and better body image compared to those assigned to laparotomy when assessed at six weeks post surgery.[12] However, differences in body image and return to work were modest, and adjusted Functional Assessment of Cancer Therapy –General (FACT-G) scores did not meet minimally important difference. At six months, there were no statistically significant differences in QOL measures other than body image, which was improved in the laparoscopy arm.

By comparison, the LACE study, which used the same QOL instruments as used in the LAP2 study (FACT-G), found QOL significantly better in the laparoscopy arm during the early post operative period and maintained to six months. Reasons for this difference are likely to be due to the high number of conversions to laparotomy in the LAP2 study, and perhaps the lower proportion of patients receiving pelvic lymph node dissection in the LACE trial TLH arm when compared to patients enrolled in the LAP2 study.[11][12]. Also, the statistical approach differed slightly. In LACE patients preoperative QOL scores were compared to their postoperative scores (patients acted as their own controls). In contrast, LAP2 compared the QOL scores of a large number of patients within a specified time period.

2.4.1.3.1 Length of hospital stay

Older retrospective, and more recent randomised trials, confirm that patients undergoing laparoscopic procedures for endometrial cancer have a shorter length of stay (LOS) despite longer operating times.[3][9][10][11] Even with a 25% conversion rate in the LAP2 trial, median length of stay was still significantly lower in the laparoscopic group compared with the open arm, with 52% of patients assigned to the (intention to treat) laparoscopy arm requiring more than two days in hospital, compared to 94% of patients assigned to the laparotomy arm (P<0.0001).[10] The most likely explanation is the significantly reduced risk of postoperative surgical adverse events as these patients experience the longest LOS.

2.4.1.3.2 Pain

Prospective single institution studies comparing LAVH to the open approach, as well as the LAP2 RCT, have shown patients experience less pain, and less need for analgesic medications when their procedure is performed laparoscopically as compared by laparotomy.[1][14][12]) The LAP2 Study assessed pain severity and pain interference with quality of life (QOL) prior to surgery, and at one, three and six weeks, and six months after surgery. Pain severity scores were lower in the laparoscopy group at one week, but not at three and six weeks or six months.[12]

In the Dutch trial there was no significant difference in reported pain between the two surgical treatment arms but significantly less pain medication was used in the laparoscopic group compared to the laparotomy group (p>0.0001).[9]

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2.4.1.4 Financial costs and cost effectiveness

Studies on cost effectiveness have had differing conclusions, depending on what costs are included. Scribner et al. compared laparoscopy to laparotomy in a non-randomised retrospective study concluding that although early discharge occurs, longer surgical time and higher anaesthetic costs offset this gain, and total costs do not differ statistically.[20] Another retrospective study found that overall costs in the laparoscopic group were significantly lower when the reduction in number of post-operative complications is accounted for.[21] An economic analysis of a multi-centre prospective randomised trial found that laparoscopic management of endometrial cancer was cost effective when compared to laparotomy based on major complication free rate as a measure of effect. TLH was more costly intra-operatively, but less costly post-operatively in hospital compared to TAH.[22]

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2.4.1.5 Disease-free and overall survival

Currently good quality data on disease-free and overall survival for patients undergoing a laparoscopic procedure for endometrial cancer is not available.[4][6][23][24] Survival data for the LAP2 trial has been presented in abstract form showing that survival curves were overlapping, thus indicating no difference in disease-free or overall survival. Survival data from the LACE trial will become available in 2014 and no survival analysis is planned for the Dutch study.[25] It seems likely that the laparoscopic approach to endometrial carcinoma will prove to be safe, but until more data are available, no firm conclusions about the oncological safety of laparoscopic approach can be made.

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2.4.1.6 Special considerations

2.4.1.6.1 TLH in the morbidly obese patient

Obesity is a well-recognised risk factor for endometrial cancer and poses significant challenges to the performance of safe surgery by any technique.

In the past, morbidly obese patients were excluded from having a TLH because of concerns regarding ventilation during general anaesthetic (particularly in the steep Trendelenburg position), obtaining surgical access, achieving pneumoperitoneum successfully, port placement, visibility into the pelvis, and lymph node sampling in this patient group.[15][26]

Some studies have shown an increased conversion rate in obese patients[10][27] and decreased success in obtaining pelvic and paraaortic lymph nodes.[28][27] Other retrospective studies (with small patient numbers) suggest that with appropriate preparation and experienced surgeons and anaesthetists, laparoscopic procedures for endometrial cancer can be performed safely in the morbidly obese, with conversion rates comparable to women with lower BMIs.[3][15][29] Some studies even suggest superiority of a laparoscopic approach in regards to surgical complications over an open procedure in the morbidly obese.[14][30]

Intraoperative anaesthetic challenges are acknowledged, in particular the adverse effects of pneumoperitoneum in the morbidly obese patient[15][31]

Unfortunately, little is known about how these adverse effects can be overcome to safely complete laparoscopic surgery in morbidly obese patients.

While there are particular technical issues associated with a laparoscopic approach in morbidly obese patients, this is the cohort of patients who potentially would benefit most from early mobilisation and the reduced wound complications conferred by a laparoscopic approach.

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2.4.1.6.2 TLH in the elderly

Another cohort that may specifically benefit from a laparoscopic approach is elderly patients. With increased age, co-morbidities are more common, and there is a higher risk of post-operative cardiac and respiratory complications, an increased risk of thrombo-embolic events, longer hospitalisation and greater loss of QOL in the post surgical period.[32] One small retrospective study showed that older patients (mean age 75 years) undergoing laparoscopic surgery for endometrial cancer had less intra-operative and post-operative complications than those having open surgery, resulting in an earlier return to normal function post-operatively.[32]

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2.4.2 Evidence summary and recommendations

Evidence summary	Level	References
Rates of conversion from laparoscopy to laparotomy depend on the laparoscopic expertise of the surgeon and the requirement to complete a pelvic and/or aortic lymph node dissection.	II, III-3	[10], [11], [13], [14], [15]
Laparoscopic pelvic and para-aortic lymphadenectomy is feasible with comparable numbers of lymph nodes being obtained by either method. Lymphadenectomy may not be feasible in morbidly obese patients.	II, III-3	[1], [4], [5], [7], [8], [10], [11], [28]
Intra-operative surgical Adverse Events (AEs) are not increased with laparoscopic management of endometrial cancer. Post-operative surgical AEs are significantly less common with laparoscopic surgery.	II	[9], [10], [11]
Operative times are longer with laparoscopy than procedures performed by laparotomy for the management of endometrial cancer.	II	[1], [10], [9], [11]
Patients undergoing laparoscopic management of endometrial cancer: *(a) Have shorter hospital stay,*	II, III-2	[3], [9], [10], [9], [11]
(b) Experience less pain, and use less pain medication,	II, III-3	[1], [9], [14], [12]
(c) Have improved surgical recovery, and quality of life in both the short and the long term to six months	II, III-3	[11], [12]
Laparoscopic approach to the management of endometrial cancer is as cost effective as laparotomy.	II, III-2, III-	[20], [21], [22]

Evidence summary	Level	References
	3	
Data from retrospective series demonstrate equivalence in disease-free and overall survival of patients undergoing laparoscopic management of endometrial cancer compared to patients undergoing laparotomy. RCT survival data are awaited.	III-2, III-3	[23], [24]

Evidence-based recommendation	Grade
Laparoscopic approach to the management of endometrial cancer can be considered by appropriately trained surgeons, as it has been found to be feasible and surgically safe with reduced post-operative complications and length of stay. Data on the oncological safety are still awaited.	**B**

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2.4.4 Supporting material

Initial literature search

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2.5 Bilateral salpingo–oophorectomy

Contents

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2.5.1 What is the evidence based surgical approach for bilateral salpingo–oophorectomy in premenopausal women with low and high risk apparent early stage endometrial cancer?

Common belief has been that uterine cancer is a disease of oestrogen imbalance, given that the risk factors are:

- Relative infertility
- Obesity
- Non-insulin-dependent diabetes mellitus

The accepted surgical management of endometrial cancer has been total hysterectomy, and bilateral salpingo-oophorectomy. So widespread is the belief that bilateral salpingo-oophorectomy is a necessary component of management, several published guidelines do not even reference its use.[1][2] Indeed, the major surgical discussion has been when, and on whom, to perform pelvic lymph node sampling.

The majority of women with uterine cancer will expect to have a good prognosis and the majority of women with uterine cancer are post-menopausal; thus, removal of the ovaries is not seen as a major concern.

However, 10% of women with endometrial cancer will be diagnosed premenopausally. For these women, premature surgical menopause will potentially seriously affect their quality of life. Thus, the merits of salpingo-oophorectomy as part of the routine surgical treatment must be carefully considered and evaluated.

Prognostic variables include stage, histological subtype and differentiation and depth of myometrial penetration. In their seminal paper, Creasman et al[3] studied 621 patients with clinical stage I endometrial cancer, looking at the surgico- pathological patterns of spread. Thirty-four patients (5%) had metastatic disease to one or both ovaries. For those with adnexal metastases, 32% had pelvic node metastases, compared with 8% positivity in those with no metastases. This study is a case collection from 43 institutions with 1180 patients enrolled, but only 621 were the subject of the paper. Although it would not be admissible as evidence by today's standards, this historic paper sets the scene for further thought.[3]

The common belief has been that uterine cancer is a disease of oestrogen imbalance. This has applied predominantly to the endometrioid histology type, as it frequently arises in a background of atypical adenomatous hyperplasia.

There is no evidence that either serous papillary or clear cell carcinomas follow this pattern.

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2.5.1.1 Premenopausal women and routine salpingo-oophorectomy

In a premenopausal woman, there may be several scenarios to consider in the evaluation and recommendation of bilateral salpingo-oophorectomy.

- Is there a risk of retaining ovaries with occult metastases?
- Is there a risk of metachronous ovarian and endometrial cancer?
- Is there a risk that continued oestrogen production might contribute to an increased recurrence rate?
- Is there a risk of Lynch Syndrome?

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2.5.1.1.1 Risk of leaving occult metastases in situ

About 5% of endometrial cancers will have synchronous ovarian disease.[3][4] This may be either synchronous primaries, or metastatic disease from the endometrium to the ovary. However, the literature is sparse, conflicting, and based on retrospective case series.[5][6] Lee et al, performed a retrospective review at a single Korean institution and found a coexisting ovarian malignancy in 19 of 261 (7.3%) women with endometrial

cancer.[5] Twelve cases were metastatic and seven were synchronous tumours. All patients had independent risk factors; for example, intraoperative extra-uterine disease, non-endometrioid histology, lymph node metastases and age >45 years. In women with no evidence of intraoperative disease, only 2 of 206 (0.97%) had ovarian disease and none were younger than 45 years of age. Their conclusion was that the risk of coexisting ovarian malignancy in women without predictable risk factors was minimal. This conclusion is consistent with the Creasman paper of 1987, which found a high correlation of ovarian metastases with positive nodal disease.

Conversely, Walsh et al conducted a retrospective chart review of 102 women between the ages of 24 and 45 who underwent hysterectomy for endometrial cancer and found that 26 patients (25%) had co-existing ovarian tumours.[6] Of these 26 cases, 23 were classified as synchronous primaries and three as metastases. The authors were not able to identify risk factors which predicted the presence of ovarian tumours. Indeed, 69% of tumours occurred in patients with grade 1 endometrial cancer and 58% in patients with less than 50% myometrial invasion. Information on the intra-operative appearance of the ovaries was available on 21 of the 26 patients with ovarian tumours. Only three of the patients (or 2.9% of the whole group) had what would be considered normal-appearing ovaries. The authors concluded that if ovaries were to be preserved at the time of hysterectomy in young women with endometrial cancer, careful assessment of the adnexa is warranted.

A population based study of 1618 women diagnosed with endometrial cancer between 1970 and 2005, identified 44 patients who were <45 years of age at the time of diagnosis.[7] Compared to the 1321 patients who were older than 45 years, the younger patients were more likely to have synchronous ovarian cancers (14% vs 2%). In the six younger patients with ovarian malignancies, five were evident at the time of surgery and only one at final pathological analysis. There was no difference in five year survival. Unfortunately, the study did not report on the presence or absence of adverse risk factors in patients with synchronous ovarian tumours.

Lee et al reviewed the Tumour Registers of 14 tertiary Korean referral hospitals to determine the outcomes of 175 patients with endometrial cancer, ranging in age from 25 to 57, who elected ovary-saving surgery. Ovary-preserving surgery was possible in 101 of the 175 women (57.7%). Median duration of follow-up was 55.0 months (range 6.2-180.0 months). Recurrence-free survival was 94.3%. Seven patients experienced a recurrence, all of whom had poor prognostic factors. None had had stage I disease. None were randomised and all were self-selected.[8]

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2.5.1.1.2 Risk of metachronous ovarian cancer in young women

Metachronous tumours are defined as those tumours which develop on multiple separate occasions. The literature in regard to development of ovarian cancer subsequent to primary diagnosis of endometrial cancer is sparse. Lee reported no metachronous tumours in 101 endometrial cancer patients who had ovarian preserving surgery and were followed for a median of 55 months. None of these studies made any reference to family history of Lynch Syndrome.[8]

2.5.1.1.3 Endometrioid cancers and risk of activation of quiescent endometrial cancer cells by endogenous oestrogen

Epidemiological studies do not support this hypothesis. Most studies are retrospective or small prospective, non-randomised studies. The only study that attempted to answer this question by randomising endometrial cancer patients to either estrogen replacement therapy or placebo, was unable to be completed.[9] It closed prematurely because of concerns regarding a decreased accrual rate as a result of the Women's Health Initiative Study results and a lower than expected recurrence rate in patients on the trial.

The risks of castration in young women are not insignificant, with increase risk of cardiovascular disease, cognitive impairment, osteoporosis, vasomotor instability and even death.[10][11][12][13][14] A large population-based cohort study of 1091 women who underwent bilateral salpingo-oophorectomy for non-cancer indications were compared to a population bases referent sample of 2383 women. The authors found that early castration (before the age of 45 years) was associated with a higher mortality for women who did not receive oestrogen.[13] A further large study reported on a subset of 10,094 women enrolled in the Nurses' Health Study, who had either oophorectomy or ovarian conservation and had never used oestrogen replacement therapy, and showed that oophorectomy before age 50, but not after age 50, was associated with a significantly increased risk of all cause mortality (HR 1.40, 95% CI 1.01-1.96).[14]

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2.5.1.2 Other histological types

There is a paucity of evidence to inform guidelines regarding extent of surgery for serous papillary and clear cell carcinomas, especially with regard to possible retention of ovaries in younger women, and none with credible level of evidence of hormone sensitivity.

2.5.1.3 Lynch Syndrome

Lynch syndrome (also known as HNPCC) is characterised by an autosomal dominant inheritance pattern, caused by a germline mutation in a mismatch repair gene. It denotes an increased risk of colorectal cancer, but gynaecological cancers are also over-represented.

Lifetime risk of endometrial cancer associated with the Lynch Syndrome varies according to the gene involved. In a recent large study of women with Lynch syndrome the risk of endometrial cancer was 54% (95% CI 20-80%), 21% (95% CI, 8%-77%), and 16% (95% CI, 8%-32%) for MLH1, MSH2 and MSH6 respectively, although estimates have varied.[15] The corresponding risks for ovarian cancer were 20% (95% CI, 1%-65%), 24% (95% CI, 3%-52%), and 1% (95% CI, 0%-3%)., but the number of MSH6 carriers was relatively small.

This increased future risk of ovarian/fallopian tube cancer warrants consideration of BSO at the time of therapeutic hysterectomy in women with early endometrial cancer either with Lynch syndrome or at-risk of Lynch Syndrome.

2.5.1.4 Conclusion

As seen from the scenarios above, there is no uniform answer to the dilemma of retention or removal of ovaries in premenopausal women with endometrial cancer.

A full discussion needs to take place, as to the risks and benefits of removal or retention of ovaries in premenopausal women who have no additional risk factors.

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2.5.2 Evidence summary and recommendations

Evidence summary	Level	References
The risk of a coexisting ovarian malignancy in young women (less than 45 years of age) with endometrial cancer is minimal (<3%), in patients who have clinically normal ovaries at the time of operation, endometrioid histology and are at low risk of lymph node metastases.	III-3	[5], [7]
Survival does not appear to be affected in young patients in whom ovaries are left in situ.	IV	[8]
Premature menopause in young women results in an increased risk of cardiovascular disease, cognitive impairment, osteoporosis, vasomotor instability and death.	III-2	[10], [11], [12], [13], [14]

Evidence-based recommendation	Grade
Consideration should be given to retaining ovaries in young women less than 45 years of age with endometrial cancer whose ovaries appear normal at operation and have no adverse risk factors.	**C**

Evidence summary	Level	References
A woman with Lynch Syndrome has up to 24% lifetime risk of developing ovarian cancer.	III-3	[15]

Evidence-based recommendation	Grade
Patients with Lynch Syndrome should be counselled that their ovaries should be removed at the time of hysterectomy given the high lifetime risk of developing ovarian cancer.	**C**

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2.5.3 References

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2.6 Lymphadenectomy

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2.6.1 What is the evidence based surgical approach for lymphadenectomy in low and high risk apparent early stage endometrial cancer?

A lymphadenectomy encompassing a pelvic lymphadenectomy (with or without a paraaortic lymph node dissection) may be performed in patients with clinical early stage endometrial cancer to:

1. Perform full surgical staging[1][2]
2. Remove bulky lymph node disease
3. Help tailor postoperative adjuvant therapy.

Lymphadenectomy can be performed as part of an open or minimally invasive procedure.

Practice point

While lymphadenectomy is part of the current FIGO 2009 surgical staging for endometrial cancer, it is important for clinicians to consider the benefits, limitations and morbidity of the procedure in the absence of compelling evidence for any survival advantage related to full surgical staging. This is of particular importance in patients who are at lower risk of nodal metastasis.

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2.6.1.1 Background

Several issues require consideration when determining the place of lymphadenectomy in clinical practice in any individual case. These are outlined below:

2.6.1.1.1 Prediction of lymph node metastasis

Some patients with apparent “early” disease are at higher risk of having more advanced surgical stage based on the presence of metastatic nodal disease and this can be predicted pre-, intra- and postoperatively based on histopathological factors and surgical findings.

Pre-operative imaging where indicated (*see related section on Pre-operative imaging*) may also predict the presence of enlarged and possibly involved nodes.

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2.6.1.1.2 Pelvic nodal involvement

The most important histopathologic risk factors to predict pelvic nodal involvement in patients with “early” endometrial cancer are high grade of tumour, deep myometrial invasion, large tumour size and the presence of cervical stromal involvement.[3]

Unfortunately, pre-operative tumour grade has been shown to correlate poorly with final postoperative histopathology findings, with only 67% of patients having their depth of invasion accurately predicted and only 58% of patients having grade of tumour accurately assessed[4] (*see section on Intra-operative assessment*). Intraoperative frozen section (where available) is better at predicting high grade rather than grade 1 and 2 disease which further hampers its use in patients with grade 1 and 2 disease who are less likely to benefit from lymphadenectomy.[4][5][6]

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2.6.1.1.3 Para-aortic nodal involvement

The risk of positive paraaortic nodes is related to the presence of positive pelvic nodes, adnexal disease and involvement of the cervix. Less than 2% of patients have isolated paraaortic nodes in the absence of positive pelvic nodes.[7] Thirty eight to fifty two (38-52) percent of patients with positive pelvic nodes and 20-57% with adnexal disease will have positive paraaortic lymph nodes[3][7][8][9] The incidence of positive paraaortic nodes directly correlates with the number of positive pelvic nodes.[10][11]

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2.6.1.1.4 Intraoperative assessment of lymph node status

Nodal palpation and frozen section are used intraoperatively to detect metastatic nodal disease. Immunoscintigraphy has also been used, but only be used in the context of research.

Intraoperative lymph node detection has a 26-36% false negative rate as more than a third of all nodal metastases are smaller than 2mm in diameter and only 7% of metastases in early cancer are larger than 2cm.[12][13][14]

Intraoperative frozen section has been proposed as a method of assessing nodal disease, however, this may underestimate the risk of nodal involvement and using this to tailor lymphadenectomy had a sensitivity of 41% and a false negative rate of 59%.[15][16] Intra-operative frozen section may be helpful in cases of clinically suspicious nodes, as a definite positive would allow the surgeon to abandon a full lymph node dissection in favour of a nodal debulking.

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2.6.1.1.5 Extent of nodal resection

The extent of lymphadenectomy has previously been standardized by the GOG (Gynecologic Oncology Group). The limits of node dissection includes the circumflex iliac vein caudally, the genito-femoral nerve on the psoas muscle laterally, the obliterated umbilical artery medially, the obturator nerve deeply and either the common iliac vessels in the case of a pelvic lymphadenectomy or the inferior mesenteric artery for a paraaortic lymphadenectomy cranially.[1]

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2.6.1.1.6 Number of nodes

Retrospective series of patients undergoing pelvic lymphadenectomy have shown that removal of ≥11 nodes in patients with high-risk histology is an independent prognostic factor for improved overall survival.[17][18]

The likelihood of detecting metastatic nodes also depends on the number of nodes removed and the superior extent of the nodal dissection.[19][20] Large series where 21 to 25 lymph nodes were removed[19] and where the superior limit of dissection went even higher than the inferior mesenteric artery to the level of the renal veins significantly increased the risk of detecting metastatic paraaortic nodal disease.[20]

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2.6.1.1.7 Laparoscopy or laparotomy for lymphadenectomy

The LAP 2 study comparing open hysterectomy and laparoscopic hysterectomy demonstrated that when compared to open lymphadenectomy, a laparoscopic approach could be performed with equivalent completeness, detection of metastatic disease, and complication rates.[21] While there was a longer operative time, the postoperative hospital stay was significantly shorter in the laparoscopic arm. Due to patient factors, a paraaortic lymphadenectomy was less likely to be performed in the open group as opposed to the laparoscopic group. A laparoscopic approach to pelvic lymphadenectomy is equivalent to laparotomy in regard to nodal number and extent of pelvic node dissection.[21]

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2.6.1.1.8 Complications of lymphadenectomy

Two large randomised clinical trials have reported the complication rate of patients undergoing open lymphadenectomy when compared to no lymph nodal dissection. Lymphadenectomy has been shown to be associated with an increased operating time, postoperative ileus, deep venous thrombosis, wound dehiscence and length of hospital stay. Not surprisingly, the incidence of postoperative lower limb lymphoedema and pelvic lymphocyst formation was significantly higher in the lymphadenectomy group.[2][22]

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2.6.1.1.9 Role of lymphadenectomy in surgical staging

Two recent randomised studies have revealed conflicting results on the ability of systematic lymphadenectomy to increase the detection rate of metastatic disease in patients with endometrial cancer. The ASTEC study noted that the incidence of nodal disease in the lymphadenectomy group (9%) was not statistically different to that observed in patients who had selective sampling of nodes.[22]

An Italian randomised controlled trial has demonstrated that lymphadenectomy is the most effective way of detecting metastatic disease with 13.3% of patients in the lymphadenectomy group having metastatic disease versus 3% in the no lymphadenectomy group[2]

One of the possible explanations for these conflicting results is the fact that mean nodal counts in the MRC ASTEC trial was low, while in the Italian study, patients were recruited only if they had more than 20 lymph nodes removed. In addition, post-operative adjuvant therapy differed between the studies.

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2.6.1.1.10 Role of lymphadenectomy in tailoring adjuvant treatment

Adjuvant treatment of endometrial cancer has traditionally consisted of pelvic radiotherapy and/or brachytherapy. A number of trials have shown that adjuvant radiation improved local recurrence rates with no effect on overall survival.[23][24][25][26][27] (*see section on Adjuvant Radiotherapy*) In addition, there is some evidence to suggest that adjuvant chemotherapy may be of some value.[28] However this remains controversial, with toxicities of combined therapies an ongoing concern (*see section on Adjuvant Chemotherapy*).

In patients with apparent early stage disease and poor prognostic factors the detection of lymph node metastases will ‘upstage’ the disease and may indicate the need for adjuvant treatment (*see related sections on Adjuvant Radiotherapy and Adjuvant Chemotherapy*) in accordance with current institutional treatment protocols.

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2.6.1.2 Impact on survival

2.6.1.2.1 Pelvic Lymphadenectomy

Two recent randomised trials have both failed to demonstrate a survival advantage in patients undergoing pelvic lymphadenectomy for apparent early stage endometrial cancer. The MRC ASTEC trial accrued 1408 patients prospectively and no survival advantage was noted after a median follow-up period of 37 months. The validity of these data has been questioned based on adequacy of nodal dissection, patient selection, indications for adjuvant therapy and significant recruitment bias in selecting patients for adjuvant treatment.[22]

An Italian randomised trial recruited patients with early stage endometrial cancer and while this study also showed no difference in progression free and overall survival, a significantly higher proportion of patients in the no lymphadenectomy group had better histologic prognostic factors.[2] The detection of metastatic disease and therefore the ability to provide prognostic information was significantly higher in patients who had lymphadenectomy.[2]

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2.6.1.2.2 Para-aortic Lymphadenectomy

Retrospective series have suggested that paraaortic nodal dissection may increase survival in patients with high-risk early stage endometrial cancer.[29][30] However, there are no randomised trials on this subject and studies are required.

2.6.1.2.3 Lymphadenectomy in patients with non- endometrioid endometrial cancer

Non-endometrioid histologic types make up 5-10% of all patients with endometrial cancers and these tumours have a significantly higher incidence of extrauterine and nodal disease and a poorer prognosis. The presence of extrauterine disease in these patients is independent of tumour size or depth of uterine invasion.[31][32][33] However, the management of these patients is limited by the absence of effective adjuvant therapies in patients with extrauterine disease.

There is currently insufficient evidence to recommend full surgical staging in patients with non-endometrioid uterine cancer. All patients with these histological subtypes should be recruited into randomised clinical trials where available.

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2.6.1.3 Conclusion

There is conflicting randomised trial based evidence on the role of lymphadenectomy in the management of women with early stage endometrial cancer. While lymphadenectomy may assist in the tailoring of adjuvant treatment in identified 'high-risk' patients there is no demonstrated long term disease specific survival advantage. More research is needed before lymphadenectomy can be strongly recommended in the management of endometrial cancer patients.

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2.6.2 Evidence summary and recommendations

Evidence summary	Level	References
Pelvic lymphadenectomy with or without paraaortic lymphadenectomy in patients with grade 1 or grade 2 endometrioid adenocarcinoma confined to the inner half of the myometrium, does not help tailor adjuvant treatment and is associated with an increased complication rate without prolonging progression free survival or overall survival.	II	[2]

Evidence-based recommendation	Grade
A simple hysterectomy and bilateral salpingo-oophorectomy may be considered optimal surgery for patients with apparent stage 1A Grade 1 or Grade 2 endometrioid adenocarcinoma of the uterus.	**B**

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Evidence summary	Level	References
Pelvic lymphadenectomy in patients with high-risk endometrial cancer confined to the uterus allows accurate staging and appropriate planning of adjuvant therapy. There is, however, no evidence that this offers a long term disease specific survival advantage.	II	[2], [22]

Evidence-based recommendation	Grade
Pelvic lymphadenectomy may be carried out in surgically fit patients with grade 3 endometrioid adenocarcinoma, deeply invasive (more than 50% myoinvasion) grade 1 and grade 2 tumours, cervical involvement, palpably enlarged nodes, or endometrioid tumours greater than 2cm, for accurate staging and appropriate planning and tailoring of adjuvant	**B**

Evidence-based recommendation	Grade
therapy.	

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Evidence summary	Level	References
Isolated paraaortic nodal involvement is uncommon. The paraaortic nodal spread of endometrial endometrioid cancer can be predicted by the presence of multiple involved pelvic lymph nodes, involvement of the uterine cervix, and adnexal involvement. The impact of a para-aortic lymphadenectomy on overall survival in patients with high-risk early stage disease without the above risk factors is not clear.	III-3	[3], [9], [7]

Evidence-based recommendation	Grade
A para-aortic lymphadenectomy may be considered in selected groups of patients with positive pelvic nodes, palpably enlarged para-aortic nodes, tumour involvement of the cervix, or adnexal disease for accurate staging and appropriate planning and tailoring of adjuvant therapy.	**C**

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2.7 Intra-operative assessment of tumour

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2.7.1 What is the role of intra-operative assessment of the uterus in low and high risk apparent early stage endometrial cancer?

In Australia, and indeed, worldwide, there is no consistent approach to the surgical management of endometrial carcinoma particularly in regard to the performance of pelvic and para-aortic lymph node dissection and/or sampling as a standard procedure. In some centres full surgical staging including nodal dissection is performed in all cases regardless of tumour characteristics unless contraindicated by factors such as medical co-morbidities or technical limitations. Conversely, some surgeons do not perform routine nodal sampling at all, with considerations for adjuvant therapy being based upon the metastatic risk determined from the final surgical-pathological findings. In general, neither of these approaches requires intra-operative assessment (IOA) of the endometrial tumour since the operative procedures would not be influenced by the results.

A third more flexible approach to surgical management restricts node dissection to those cases that are considered 'high-risk' (HR) for metastases. In this context HR designation may be based upon pre-operative findings, in particular the diagnosis of high-grade endometrioid adenocarcinoma or high-risk histologic types on endometrial sampling, or on the operative disclosure of obvious extra-uterine disease. Again IOA is usually not required in this setting since full staging would be performed unless otherwise contra-indicated. Generally, therefore, IOA is used to identify those patients with (apparent) low-stage and low-grade endometrioid adenocarcinomas who have adverse prognostic features identified only at operation.

Factors that have been used to assign tumours to the high risk category include high-grade histology or tumour subtype, deep (>50%) myometrial invasion, cervical invasion, larger tumour size (>2cm), and/or the presence of lympho-vascular space invasion (LVSI).[1][2][3]

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2.7.1.1 Basis of current review

Studies of IOA of endometrial carcinoma were initially identified from the literature search. Studies available only in abstract form were excluded. In total, 21 published studies that included from 31 to 403 patients were assessed.[4-24]

The overall quality of the studies was poor with most studies being retrospective, non-consecutive, non blinded (to reference standard) reviews (ie level III-2 evidence). Only three studies were level II evidence. Of those, one had an independent blinded comparison to a reference standard using consecutive patients, but patients with complex atypical hyperplasia (CAH) were included.[4] A second study reported on 64 consecutive patients with endometrial cancer in whom depth of invasion was assessed by a pathologist blinded to the frozen section result.[5] The third study was a retrospective review, however, it was reported that all patients were included, blinding was used and information was available on all patients.[6]

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2.7.1.2 Methods of intra-operative assessment

Intra-operative assessment of HR features in endometrial carcinoma may be based upon either gross or histological (frozen section) examination of the hysterectomy specimen. Cervical involvement and depth of myometrial invasion may be assessed naked eye (by the surgeon and/or the pathologist) or microscopically, whereas assessment of tumour type, grade and LVSI require frozen section. The use of different IOA methods (gross or histological) in different centres probably partly reflects the availability of pathology services locally.

Methods of intra-op assessment:

1. Gross visual inspection (GVI) of tumour invasion
2. Microscopic (frozen section) assessment of high risk features (tumour invasion, grade of tumour, histologic type or lymphatic space invasion)

2.7.1.2.1 Gross visual inspection (GVI)

Twelve groups have reported their experience with gross visual inspection (GVI) of myometrial invasion in a total of 2083 patients.[7] [8] [9][10] [11] [12] [13] [14] [15] [16][17] [18] Inclusion criteria varied with respect to histologic tumour type and grade as well as stage of disease. Accuracy in predicting myometrial invasion varied from 80% to 90%, with a sensitivity of 65% to 80%. The depth of invasion was underestimated in 15% to 27% of patients and overestimated in 2% to 17% of patients.

Accuracy of GVI of myometrial invasion is influenced by grade, size and histologic variant of the tumour. Accuracy is best with low grade tumours and tumours less than 2 cm and worse with grade 3 tumours, aggressive histologic variants or tumours with multiple foci.[7] [11] [12][13][14] Accuracy for grade 3 tumours was reported as less than 60% in one study [7]. Overestimation of depth of invasion occurred most often in patients with adenomyosis and leiomyomas.[11]

Several groups have also reported their experience with GVI of cervical involvement with tumour.[6] [11] [14][18] Accuracy ranged from 79% to 97% but sensitivity was as low as 32% in one study.[11] The extent of involvement was underestimated in 11% to 67% of patients. The clinical implications of determining cervical invasion intra-operatively is unclear given that optimal therapy for stage 2 disease has yet to be defined.

Frumovitz combined pre-operative tumour grade and intra-op assessment of gross tumour invasion in order to try and predict those who were at increased risk for lymph node metastases and therefore requiring lymphadenectomy.[9] One hundred and fifty three patients with either grade 1 or 2 endometrioid tumours and intra-operative assessment of myometrial invasion of <50% were compared to the final pathology using a predictor score. Pre-operative tumour grade was upgraded in over 20% of patients on final pathology. The depth of invasion was greater than 50% in 21% of grade 1 and 32% of grade 2 tumours. The authors concluded that the combination of pre-operative grade of tumour and intra-operative gross myometrial invasion was a poor predictor for extrauterine disease.

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2.7.1.2.2 Microscopic (frozen section) assessment

Nine authors have reported on their experience with frozen section assessment of myometrial invasion in a total of 1035 patients.[19][20][21][22][4][5][16][17][23] As with the studies of GVI, these studies were also mostly retrospective reviews of varying sizes (between 31 and 318 patients).

In the best designed study, Case prospectively evaluated in a blinded fashion, 60 consecutive patients with either complex atypical hyperplasia or endometrial cancer on whom frozen section for myometrial invasion was performed.[4] Accuracy for frozen section was 67% with clinically significant upgrading in 18% of patients. Similarly, Ozdemir reported on 64 consecutive patients with endometrial cancer who had intra-operative frozen section assessment of myometrial invasion in a blinded fashion.[5] Accuracy of frozen section for deep myometrial invasion was 80%.

Others have conducted retrospective, non blinded, non-consecutive reviews and have reported an accuracy of 80% to 95%.[19][20][21][22][16][17][23] Myometrial invasion was underestimated in 3% to 19% and overestimated in 2% to 8%, (usually because of the presence of adenomyosis or deep lymphatic space tumour emboli).[19][20][22]

In addition to frozen section assessment of myometrial invasion, some authors have reported on frozen section assessment of grade of tumour, as compared to final pathology. The accuracy of frozen section grading of tumours ranges from 58% to 86%.[19][20][22][4][23] Grade of tumour was underestimated in 8% to 38% of patients and overestimated in 4% to 6 % of patients. Case reported that it was grade 1 tumours that were most often upgraded whilst Kucera reported that accuracy of grading was poorest for grade 2 and 3 tumours.[4][23]

One study has attempted to assess all high risk parameters (depth of invasion, tumour grade, cervical invasion, histological subtype and lymphatic space invasion) in a retrospective review of 318 pts with endometrial adenocarcinoma who underwent frozen section of both myometrium and cervix.[24] Based on specific parameters, the patients were divided into low risk and high risk groups. They found that intra op frozen section results corresponded with final pathology in 95% of cases, giving a PPV of 99% and a NPV of 92% and concluded that intra-operative frozen section was a reliable and applicable tool in assessing risk. However identification of high risk patients who then subsequently underwent lymphadenectomy did not translate into improved survival.

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2.7.1.3 Summary of findings

The depth of myometrial invasion, presence of cervical invasion, and histological grade/ type are the factors that have been assessed most commonly intra-operatively with overall accuracies of approximately 80% to 90%, 84% to 99%, and 85% to 90% respectively (compared to final histological assessment deemed to be the ‘gold standard’).[4-24] The reported accuracies for macroscopic and microscopic assessment of myometrial invasion are similar. Several studies have noted that the depth of myometrial invasion is more accurately

determined in low-grade tumours[7][11][12] where such assessment is likely to be more relevant. Most investigators have interpreted their findings to be supportive of the practice of IOA in endometrial carcinoma. However, others have expressed concern that the diagnostic accuracy is not sufficient to influence operative management.[7][9][21] Since most intra-operative errors lead to under-grading or under-staging (compared with final assessment), it has been argued that complete surgical staging should be performed in all endometrial carcinomas.

Practice point
Intra-operative assessment may be used to identify those patients with (apparent) low-stage and low-grade endometrioid adenocarcinomas who have adverse prognostic features identified only at operation.

2.7.1.3.1 Difficulties in assessment of the literature and evaluation of the role of intra-operative assessment in endometrial carcinoma

A fundamental problem in making recommendations about IOA of endometrial tumours is that the optimal surgical management remains controversial (*see section on Lymphadenectomy*). Thus, the impact of IOA depends on individual surgeons own threshold for performing lymphadenectomy or complete surgical staging.

Even in situations where IOA is used, there appears to be variation regarding its principal role, and this influences the interpretation (and potential significance) of diagnostic errors. In those cases where it is primarily used to determine which patients could avoid lymphadenectomy, the false negative rate could be regarded as a more significant error than the over-diagnosis of myometrial invasion or tumour grade ('false positive' error) since the default surgical procedure would include nodal dissection. Conversely, in those situations where it is used to determine who should have a full surgical staging (the default position being to avoid lymphadenectomy), an over-diagnosis ('false positive' error) could be considered to be more serious than under-diagnosis. Thus, while details such as the overall accuracy, specificity and sensitivity, and positive and negative predictive values of IOA are provided in many studies, few authors have specifically addressed the implications of erroneous diagnoses in their own practice.

There are major differences in case selection in the published series with a variable proportion of tumour subtypes and grades. Only one study is restricted to endometrioid adenocarcinoma (and its variants);[21] three studies do not comment upon tumour type.[20][6][10] The proportion of non-endometrioid carcinomas, most of which will fall into the high-grade category, will influence the accuracy and relevance of the IOA findings.

The reviewed studies were published between 1996 and 2010 and, not surprisingly, most use the previous FIGO staging system. Therefore usually it is not possible, based upon the available data, to extrapolate the findings to the 2009 FIGO staging system.

The macroscopic and histological features used to designate HR tumours (deep myometrial invasion, high-grade or aggressive histological subtype, gross cervical invasion, and LVSI) are inter-related and thus many tumours will be positive for more than one of these factors. However, this has seldom been taken into account so that in

most studies it is not clear whether the apparent false negative or false positive rate using one particular feature (for example, depth of myometrial invasion) was clinically relevant. This point is illustrated in the study by Quinliven and colleagues who did assess the clinical implications of their erroneous IOA findings.[22] They describe four patients in whom IOA falsely suggested deep myoinvasion but since all of these tumours were also high-grade histological subtypes, lymphadenectomy was appropriately performed according to local guidelines.

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2.7.1.3.2 Logistic problems of intra-operative assessment

Apart from the potential diagnostic limitations of the type of IOA, the procedure is also associated with some operative delay, estimated to be 3-5 minutes for macroscopic assessment alone,[8] and from 10-16 minutes[24] or up to 30 minutes when frozen section is employed.[19] As with all frozen section procedures, the use of IOA in endometrial carcinoma also has logistic implications for histopathology departments in terms of pathologist/ scientist's time, and the potential disruption and delay to the routine diagnostic services.

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2.7.2 Evidence summary and recommendations

Evidence summary	Level	References
The depth of myometrial invasion, presence of cervical invasion, and histological grade/ type are the factors that have been assessed most commonly intra-operatively with overall accuracies of approximately 80% to 90%, 84% to 99%, and 85% to 90% respectively (compared to final histological assessment deemed to be the 'gold standard')	III-2	[24], [7], [8], [9], [19], [20], [6], [10], [11], [12], [21], [22], [13], [14], [4], [5], [15], [16], [17], [18], [23]
However, the quality of the studies are poor with only three studies using consecutive patients with an independent blinded comparison to final histopathology.	II	[6], [4], [5]

Evidence-based recommendation	Grade
Caution should be exercised in relying on intra-operative assessment of depth of invasion, involvement of cervix and histological grade as a means to determine extent of surgical staging	**C**

Evidence summary	Level	References
Measurement of depth of myometrial invasion using either gross visual assessment or frozen section is less accurate when dealing with high grade, histological aggressive or larger tumours	III-2	[7], [12], [13], [14]

Evidence-based recommendation	Grade
Patients with high grade, histologically aggressive or large tumours are unlikely to benefit from intra-operative assessment.	**D**

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2.7.3 References

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2.7.4 Supporting material

Initial literature search

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2.8 Radiotherapy

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2 Evidence summary and recommendations
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2.8.1 After hysterectomy, what is the role of radiotherapy (external beam, brachytherapy) in the management of early stage high risk endometrial cancer?

These guidelines will focus on the role of adjuvant radiotherapy in women with stage I and II (FIGO 2009)[1] endometrial cancer. It includes adenocarcinoma as well as papillary serous and clear cell carcinoma histological subtypes.

Endometrial cancer is the most common female genital tract malignancy. Most patients diagnosed have early stage disease. Research to date into adjuvant treatments for early stage endometrial cancers has only shown an improvement in loco-regional recurrence rate and there is only a trend towards improvement in overall survival in the higher risk groups.[2][3][4][5]

There is a lack of well-conducted randomised controlled trials to confidently direct adjuvant treatment decisions. Most data has been derived from retrospective reviews and other observational studies. This has resulted in a great deal of variability in the use of adjuvant radiotherapy for early endometrial cancer in Australia and around the world. If radiotherapy treatment options were more standardised, this would result in more consistent practice and improve the data available for research.[6][7] When there are no definitive studies to advise on the best treatment, the recommended treatment should be based on combined expert opinion.

There are a number of other factors that have made the development of evidence-based guidelines difficult for endometrial cancer.

The International Federation of Gynecology and Obstetrics (FIGO) released new staging guidelines for endometrial cancer in 2009.[1] Published data to date have however been based on the older FIGO 1988 staging system. This makes it harder to directly translate this data into current recommendations based on the new staging system.

Inconsistent reporting of histology of endometrial cancers has made comparing trials more difficult with more recent trials now requiring central pathology review.[8] While there are histological subtypes, including uterine papillary serous carcinomas (UPSC) and clear cell carcinomas (CCC), that are recognized to be more aggressive with a poorer prognosis, for endometrial adenocarcinomas the stratification of prognostic factors is more problematic.

Additionally, there are many prognostic risk factors that have been identified. These include patient age, lymphovascular invasion (LVI), the ratio of myometrial/stromal invasion to total myometrial thickness and tumour grade.[2][3][4][9] However, there is no concordance regarding the definition of intermediate and high-risk disease based on these risk factors both nationally and internationally. This makes interpretation of the published data more difficult.

There is variation in the type of adjuvant radiotherapy used for early endometrial cancer in Australia and internationally. The most commonly used methods of delivering radiation are multifield external beam radiotherapy to the pelvis (pelvic EBRT) and vaginal brachytherapy (VBT). Whole abdominal radiation (WART) has been used for the high-grade histological subtypes.[10][11]

There is also a great variability in the prescribed dose of radiotherapy with VBT dosing having the largest variation. The most widely accepted dose for pelvic EBRT in Australia is 45-50.4 Gy in 1.8-2 Gy per fraction, five fractions per week. Vaginal brachytherapy prescribing is more contentious and there is a wide variability in practice across Australia.[6] The dose for VBT used alone ranges from 30-40 Gy in four to six fractions. The dose for VBT used in combination with pelvic EBRT ranges from 12-18 Gy in two to three fractions.

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2.8.1.1 Stage 1 endometrial cancer

There is a lack of data to support the routine use of adjuvant treatment in uterine cancer confined to the pelvis. There is evidence that adjuvant radiotherapy does improve local control in patients at high risk of recurrence.[2][3][4][5][9][12][13] The decision to treat should be made on an individual basis after considering local control and toxicity issues and after discussion with the patient.

A number of trials have shown that in early stage endometrial cancers adjuvant radiation improved local recurrence rates with no effect on overall survival - PORTEC-1,[2] GOG99,[3] MRC ASTEC and NCIC CTG EN.5[4] and Aalders et al.[9] PORTEC-1 and GOG99 used pelvic EBRT alone. Aalders et al compared VBT to VBT and pelvic EBRT and found that the additional pelvic EBRT was only necessary in the high-risk groups. The MRC ASTEC and NCIC CTG EN.5 trials found that VBT alone may be just as effective for local control as compared to pelvic EBRT. A lymphadenectomy rate varied between these trials and was only routinely performed in GOG99.

A number of meta-analyses of these randomised trials have also confirmed the local control benefit.[4][5][12] These meta-analyses support the use of adjuvant radiation in the intermediate to high-risk groups, and not in the low risk patients. Kong et al[12] also showed a trend towards improved survival in the high-risk group stage 1C (FIGO 1988) and grade 3 pathology group on subgroup analysis. Johnson et al[5] also demonstrated a potential survival benefit in the high-risk group with stage 1C and grade 3 pathology. Blake et al[4] in the most recent meta-analysis does not support any overall survival benefit with pelvic EBRT.

PORTEC-2[8] compared outcomes of pelvic EBRT to VBT alone. The study group included stage 1 or 2A endometrial cancer with features of high and intermediate disease:

1) age greater than 60 years and stage 1C grade 1 or 2 disease, or stage 1B grade 3 disease; and

2) stage 2A disease, any age (apart from grade 3 with greater than 50% myometrial invasion).

There was no significant difference in loco regional recurrence rates. There was less toxicity with VBT alone. UPSC and CCC as well as stage 1C grade 3 endometrial adenocarcinoma were all excluded from this study.

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2.8.1.2 Stage 2 endometrial cancer

Presentation with stage II endometrial cancer is uncommon. There is a lack of evidence to determine optimal adjuvant treatment for this group with only observational data available, as there is no prospective data published.

There are a number of small retrospective reviews that support the use of VBT alone in those stage 2 patients that have been completely surgically staged.[14][15][16][17][18][19] There is a reduction in toxicity with this approach with similar local control compared to historical controls treated with pelvic EBRT. Randomised trials are needed to confirm this.

Local recurrence rates after surgery and adjuvant radiation (using a combination of pelvic EBRT and VBT) are low when tailored to surgical and pathological features.[14][20] These prognostic features include cervical involvement, the ratio of myometrial/stromal invasion to myometrial thickness, grade and extent of surgery.

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2.8.1.3 Uterine papillary serous cancer and clear cell carcinoma

Uterine papillary serous cancer (UPSC) represents approximately 10% of all uterine cancer diagnoses, but is responsible for a disproportionate number (nearly 40%) of uterine cancer deaths.[21]

With UPSC the prognostic significance of complete surgical staging including the extra-uterine features is important. It is not uncommon to find extra-uterine disease without any sign of myometrial invasion.

UPSC has a propensity to spread to peritoneal surfaces similar to ovarian serous cancers. Unlike early endometrial adenocarcinoma where recurrence is more likely in the local area including vagina and pelvis, UPSC tends to recur outside the pelvis and in multiple sites. There are conflicting data for the use of WART. There have been no convincing studies to support whole abdominal radiation (WART) over pelvic EBRT with many recurrences occurring within the abdominal field.[22][23][24][25][26] There are however other studies that do support the use of WART.[10][11] Currently there is no consensus on the use of WART. The benefit of chemotherapy will be discussed elsewhere.

Clear cell carcinoma (CCC) represents around 1-6% of all uterine cancers. There is a paucity of data on which to formulate guideline recommendations. Some data have suggested that CCC is not as aggressive as UPSC and behaves more like a poorly differentiated endometrial cancer.[27] **Due to the lack of data, CCC should still be treated like UPSC.**

2.8.1.3.1 Recommended treatment algorithms

Adjuvant treatment for Stage 1A (FIGO 2009)

* If other high risk factors present ie LVI, age >60), see evidence summary box.
# See recommended VBT protocol
[m] If any other risk factors present could consider adjuvant VBT
[o] see chemotherapy recommendation

Adjuvant treatment for Stage 1B (FIGO 2009)

* If other high risk factors present i.e. LVI, Age >60), see evidence summary box.
# See recommended VBT protocol
[N] consider if multiple high risk factors
[m] see chemotherapy section recommendations.

Adjuvant treatment for Stage 2[L] (FIGO 2009)

* If other high risk factors present i.e. LVI, age >60), see evidence summary box.
# See recommended VBT protocol
[N] consider if multiple high risk factors
[m] see chemotherapy section recommendations.
[L] little evidence for stage 2 disease, early stage 2 was included in some early stage studies.

2.8.2 Evidence summary and recommendations

Evidence summary	Level	References
For apparent stage 1 endometrial cancer with intermediate/high risk features, there is a local control benefit to pelvic EBRT (6% absolute), but no overall survival benefit.	I, II, IV	[2], [3], [4], [5], [9], [12], [13]

Evidence-based recommendation	Grade
Adjuvant radiation can be offered to those stage 1 patients with risk factors in order to improve local control.	**B**

Evidence summary	Level	References
Equivalence is seen between VBT and pelvic EBRT for local control. There is less toxicity with VBT use. (See inclusion criteria Table 1.)	II, IV	[4], [8], [18]

Evidence-based recommendation	Grade
In selected at-risk patients, use of VBT alone over pelvic EBRT can be considered to reduce toxicity.	**B**

Evidence summary	Level	References
For apparent stage 1 and 2 disease, VBT using 21 Gy in 3 fractions (PORTEC 2 protocol) showed equivalence in locoregional control to pelvic EBRT.	II	[8]
Increased toxicity occurred when VBT dose exceeded a dose equivalent to 60 Gy in 2 Gy per fraction. Doses lower than this showed acceptable local control rates.	IV	

Evidence-based recommendation	Grade
It is reasonable to follow the PORTEC-2 dosing guidelines for adjuvant brachytherapy. The equivalent VBT dose should be limited to below 60 Gy/2 Gy per fraction.	**D**

Evidence summary	Level	References
There is a small (5% absolute) improvement in pelvic control when EBRT is added to VBT in stage 1 disease. There is an associated increased toxicity. There is no overall survival benefit.	II	[9]

Evidence-based recommendation	Grade
The addition of EBRT to VBT in higher risk patients with early stage disease can be considered in order to improve local control. For combined VBT and pelvic EBRT, PORTEC-3 Guidelines can be used to guide radiotherapy dosing.	**C**

Evidence summary	Level	References
In patients with stage 2 tumours, using combined pelvic EBRT and VBT results in local control rates with acceptable toxicity.	IV	[14], [20]
VBT without pelvic EBRT for surgically staged 2 disease results in comparable local control rates and reduced toxicity.	IV	[14], [15], [16], [17], [18], [19]

Evidence-based recommendation	Grade
Patients with apparent stage 2 tumours, combined use of EBRT and VBT is recommended. In	

Evidence-based recommendation	Grade
those patients with stage 2 (full surgical staging), VBT alone can be considered.	**D**

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Table 1: Risk factors to consider for adjuvant radiotherapy based on published trials.

Trial	Risk Factors
Aalders	*Age >60, >50 % MMI along with Grade 3
Keys' (GOG99)	*High-intermediate risk group (1) moderate to poorly differentiated tumour, presence of lymphovascular invasion, and outer third myometrial invasion; (2) age 50 or greater with any two risk factors listed above; or (3) age of at least 70 with any risk factor listed above. stages 1B, 1C, and 2 (occult disease) were included.
Creutzberg (PORTEC-1)	* High risk; 60 and over with deeply invasive grade 1–2 tumours or superficially invasive grade 3 tumours. NB 1C G3 excluded in this trial.
Nout (PORTEC-2)	^ High-intermediate risk: (1) age greater than 60 years and stage 1C grade 1 or 2 disease, or stage 1B grade 3 disease; and (2) stage 2A disease, any age (apart from grade 3 with greater than 50% myometrial invasion) (no UPSC or CCC)
Blake (ASTEC/EN.5)	*FIGO stage 1A and 1B grade 3; 1C all grades; papillary serous; or clear cell histology all stages and grades, and 2A included.

*Pelivc EBRT
^ VBT,
MMI myometrial invasion.

Table 2: Suggested VBT dosing guidelines based on PORTEC-2 and PORTEC-3

	Dose & Fractionation	Interval between treatments	TYPE	Prescription Point	Length of vagina covered by reference dose
VBT alone	21Gy/3 #	1 week	HDR	5mm from cylinder surface	Proximal 3 cm/ upper 1 /3-1/2
VBT (with EBRT)	10Gy/2 # or any combination EDQ2 60Gy	At least 3/7 apart. Total treatment completed in 50 days	HDR	5mm from cylinder surface	Proximal 3 cm/ upper 1 /3-1/2

*Dose distributions should be obtained, and the dose in the bladder and rectum reference points should be computed (according to ICRU-38).

EDQ2 –equivalent dose to 60 Gy in 2 Gy per fraction when converted.

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2.8.3 References

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2.8.4 Supporting material

Initial literature search

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2.9 Chemotherapy

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2.9.1 After hysterectomy, what is the role of chemotherapy (concurrent /concomitant, sequential, sandwich, chemoradiation) in the management of early stage high risk endometrial cancer?

Endometrial cancer rates are increasing as obesity rates climb in developed countries such as Australia, where endometrial cancer is now the third commonest cancer affecting women.[1][2] It is predominantly diagnosed in post-menopausal women many of whom present early with bleeding and have stage 1 disease that is highly curable, with an overall long-term survival rate of 80%. However, once disease has spread to involve the deep myometrium, the uterine cervix or beyond (FIGO stage II and above), overall survival rates drop down to 65% and below. Standard post-operative therapy consists of radiotherapy which lowers the risk of local relapse but does not increase survival rates as most deaths occur due to the development of distant metastatic disease.

Although there is some evidence to suggest that adjuvant chemotherapy may be of value, the place of adjuvant chemotherapy remains controversial and as yet no large randomised trial has conclusively demonstrated an overall survival advantage if used in addition to radiotherapy. The relative paucity of high-quality evidence and lack of level 1 evidence means that opinions are divided and recommendations must be made with caution. In order to give women with this disease the best chance of survival it is important to consider all aspects of available evidence and present a balanced view.

In this section the term ‘adjuvant’ chemotherapy is used to refer to chemotherapy given after surgery that results in no visible macroscopic disease. The term adjuvant is not used for the treatment of residual macroscopic disease post surgery, or the treatment of stage IV disease.

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2.9.1.1 Identification of patients at higher risk of relapse

It is possible to identify a group of patients who are at high-risk of developing relapsed disease at distant sites after initial surgery, despite the use of standard adjuvant pelvic radiotherapy. Important prognostic features that are reflected in the FIGO surgical staging system include the depth of myometrial invasion, the grade of the tumour and the presence of pelvic or para-aortic lymph node involvement.[3][4][5] Lymphovascular space invasion has also been found to be a major prognostic factor which significantly and independently increases the risk of relapse, especially distant relapse.[6][7][8] The histological subtype of disease is also important. Serous and clear cell cancers, which comprise up to 10% and 5% of endometrial carcinomas, respectively, have an inferior prognosis due to aggressive growth and frequent presentation at a more advanced stage.[9]

The five year survival rates for endometrial cancer as a whole, based on the most recent FIGO data are shown in Table 1 below:

Table 1: 5 year overall survival for selected FIGO 2008 stages and grade of endometrial cancer*

Stage and grade	Description	5 year overall survival (%)
Stage IB, grade 1	Tumour confined to the myometrium, with invasion equal to or more than half of the myometrium	91
Stage IB, grade 2		86
Stage IB, grade 3		75
Stage II, grade 1	Tumour invades the cervical stroma, but does not extend beyond the uterus	81
Stage II, grade 2		77
Stage II, grade 3		65
Stage IIIA, grade 1	Tumour invades the serosa of the corpus uteri and/or adnexae	83
Stage IIIA, grade 2		71
Stage IIIA, grade 3		45

Stage and grade	Description	5 year overall survival (%)
Stage IIIB, grade 1	Vaginal and/or parametrial involvement	75
Stage IIIB, grade 2		45
Stage IIIB, grade 3		31
Stage IIIC, grade 1	Metastases to pelvic and/or para-aortic lymph nodes	67
Stage IIIC, grade 2		61
Stage IIIC, grade 3		51

* Based on the 26th volume of the FIGO annual report of the treatment of carcinoma of the corpus uteri[10]

2.9.1.2 What evidence exists regarding the role of chemotherapy?

2.9.1.2.1 Retrospective data

Multiple influential retrospective reports about the experience of using adjuvant chemotherapy have been published. Unfortunately the role of selection bias inherent in all of these retrospective studies is a major confounding variable making it impossible to provide high-quality recommendations for the treatment of women on the basis on these data. Some of the larger reports are described in the Appendix.

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2.9.1.2.2 Randomised controlled trials comparing the use of adjuvant chemotherapy alone with the use of adjuvant radiotherapy alone

Several prospective randomised trials involving adjuvant chemotherapy have been performed. Unfortunately, the results are not conclusive, with many of the studies being under powered and having significant variation in eligibility criteria as well as the nature of the control and intervention arms. Three trials have compared the use of adjuvant chemotherapy alone with the use of adjuvant radiotherapy alone.[11][12][13] Two of these trials, from Italy and Japan, showed no difference in survival outcomes between the two treatments, while the GOG122 study suggested a survival benefit from adjuvant chemotherapy in women with stage III and IV disease compared to the use of whole abdominal radiotherapy alone.[11][12][13] The full results of these trials are described in detail in the Appendix, and also summarised in Table 2.

Of note, the pelvic recurrence rate was high (up to 18%) in the chemotherapy alone arm of the GOG122 trial. However, this trial suggests that there is a role for chemotherapy in the treatment of women with advanced endometrial cancer, particularly those who are incompletely staged or have residual disease at the completion of surgery. However, the role of chemotherapy in the treatment of women with stage III disease and no macroscopic disease at the completion of surgery is uncertain given the negative results of the Italian trial in which two thirds of the patients had stage III disease.

Table 2: Randomised trials comparing adjuvant chemotherapy with adjuvant radiation treatment

Author	Eligible patients	Patient numbers	Treatment arms	5year PFS	5year OS	Comments
GOG122 Randall et al[11]	Stage III-IV disease of any histology. Residual disease less than 2cm allowed	202 194	WAI Cisplatin and doxorubicin x 6	38% 50% P < 0.01	42% 55% P < 0.01	Chemotherapy superior but associated with more toxicity WAI not optimal RT No clear benefit with serous histology
Italian study Maggi et al[13]	FIGO 1988 stage IC grade 3, stage II grade 3 with > 50% myometrial invasion or stage III Serous or clear cell excluded	166 174	Pelvic XRT Cyclophosphamide, doxorubicin and cisplatin x 5	63% 63% P = ns	66% 69% P = ns	No significant difference in survival outcomes. Trend suggesting chemotherapy lowered distant relapse and XRT lowered local relapse
JGOG-2033	FIGO 1988 stage IC – IIIC endometrioid endometrial cancer	193	Pelvic XRT	83.5% 81.8%	85.3% 86.7%	No difference in survival outcomes. Post-hoc analysis suggested improved survival with chemotherapy in a 'high-

Author	Eligible patients	Patient numbers	Treatment arms	5year PFS	5year OS	Comments
Susumu et al[12]	with > 50% myometrial invasion	192	Cyclophosphamide, doxorubicin and cisplatin x 3	P = ns	P = ns	intermediate' risk group but not in those with 'high' risk disease

Abbreviations: PFS – progression free survival, OS – overall survival, WAI – whole abdominal irradiation, XRT – Radiotherapy, ns – not significant

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2.9.1.2.3 Randomised controlled trials comparing sequential adjuvant chemotherapy and radiotherapy to adjuvant radiotherapy alone

Four trials have compared the use of pelvic radiotherapy alone with a combination of chemotherapy and pelvic radiotherapy treatment (table below).[14][15][16] None of these trials have demonstrated a statistically significant improvement in overall survival with the addition of adjuvant chemotherapy to radiotherapy. However, all of the trials are small and underpowered to detect an overall survival difference, with two trials (ILIADE-III and GOG 34) closing prematurely due to poor accrual. The full results of all of the individual trials are described in the Appendix.

Author and year of publication	Eligible patients	No	Treatment arms	5year PFS	5 year OS
GOG 34 Morrow et al [14] 1990	Clinical stage I or II with ≥1 high risk factor	89 92	Pelvic RT Pelvic RT followed by doxorubicin x 6	-	61% 66% P = ns
Finnish trial Kuoppala et al [15] 2008	FIGO 1988 stage IA-IB grade 3 or stage IC-IIIA of any grade	72 85	Split-course Pelvic RT Sequential cisplatin, adriamycin, cyclophosphamide x3 plus split-course pelvic RT	Median18mo Median25mo P = ns	84.7% 82.1% P = ns
NSGO-EORTC Hogberg etal [16] 2010	Stage I-III disease including serous and clear cell histology. No residual macroscopic disease	191 187	Pelvic RT Pelvic RT with various types of chemotherapy x 4 before or after	72% 79% P = 0.04	76% 83% P = ns

ILIADE-III Hogberg et al [16] 2010	FIGO 1988 stage IIB or III disease. Serous and clear cell histology excluded	76 80	Pelvic RT Doxorubicin and cisplatin X3 followed by pelvic RT	61% 74% P = ns	73% 78% P = ns
Pooled NSGO and ILIADE-3 Hogberg et al [16] 2010	As above	267 267	Pelvic XRT Pelvic XRT plus chemotherapy	69% 78% P = 0.009	75% 82% P = ns

Split course Pelvic RT: 28Gy each separated by a pause of three weeks

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2.9.1.2.4 Combined analysis of MaNGO and NSGO/EORTC trials

The results of two trials ILIADE-III and NSGO-EORTC, which were individually underpowered, have been presented in a single combined publication with an analysis of pooled results.[16] Although the trend in both of these trials is for a benefit from the use of adjuvant chemotherapy, there was still a lack of an overall survival benefit in the pooled results. It is unclear if this has occurred because of lack of power or because not all of the very variable treatments used in the NSGO/EORTC trial have an equal effect, with most patients receiving older-style doxorubicin and cisplatin chemotherapy and the radiotherapy not being standardised. In subset analysis, there appeared to be similar treatment effects with regard to age, grade, stage, or whether or not a lymphadenectomy was performed. However, there was an apparent lack of benefit in patients with serous and clear cell carcinomas.

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2.9.1.2.5 Randomised controlled trial comparing two different adjuvant chemotherapy regimens post adjuvant radiotherapy

2.9.1.2.5.1 GOG184

The GOG184 study compared a primary endpoint of relapse-free survival using two different adjuvant chemotherapy regimens (cisplatin and doxorubicin versus cisplatin, doxorubicin and paclitaxel [TAP]) given to 522 eligible randomised patients.[17] Further details are described in the Appendix. After a median follow-up of 47 months these was no difference in the primary outcome of the relapse free survival rate between the two groups (62 versus 64%; p = 0.21), despite this regimen being more active in the setting of advanced endometrial cancer.[18] Survival data are not yet mature for final analysis; however the trial results so far would not support the use of TAP chemotherapy in the adjuvant setting given its significant toxicity.

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2.9.1.2.6 Data about which chemotherapy is most active in the adjuvant treatment of endometrial cancer

Limited data is available about what is the most active chemotherapy treatment in the adjuvant setting, as the trials described earlier have used a range of different regimens. Single-agent treatment does not appear to be effective. The trials that have suggested some benefit from the use of adjuvant chemotherapy have used cisplatin and doxorubicin, or also allowed platinum-containing doublets such as carboplatin plus paclitaxel.[16] Trials performed in the metastatic setting, including a meta-analysis, have determined that the addition of anthracyclines (e.g. doxorubicin) or taxanes (e.g. paclitaxel) to cisplatin increases the response rate, although leads to greater toxicity.[9][19] A randomised GOG trial comparing doxorubicin and cisplatin (AP) therapy with adriamycin, cisplatin and paclitaxel with filgrastim support (TAP) for women with measurable stage III, stage IV or recurrent endometrial carcinoma showed an improved response rate (57% versus 34%) and a significantly longer median survival of 15 versus12 months (58% versus 50% one-year survival) for TAP.[18] About half of the women in this trial had received prior radiotherapy to the pelvis. However the TAP regimen resulted in significantly increased neurotoxicity and may not be suitable for older patients.[18] Doxorubicin and paclitaxel is not superior to doxorubicin and cisplatin.[20] Carboplatin and paclitaxel therapy appears to be as effective and less toxic than AP or TAP, based on single arm studies, and may be more suitable for older patients.[21][22][23] A GOG trial addressing this question by comparing carboplatin and paclitaxel with TAP in metastatic disease has recently completed accrual.

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2.9.1.2.7 Data available about the role of chemo-radiation in adjuvant therapy

The rationale for the addition of concurrent platinum-based chemotherapy to adjuvant radiotherapy to the pelvis is based on the premise that it should further improve local control rates by sensitising tumour cells to the effects of irradiation. The approach of combining platinum-based chemotherapy with radiotherapy has

proven to increase treatment efficacy in a number of tumour types including head and neck, esophageal and cervical carcinomas. Four pilot studies have indicated concurrent radiotherapy and chemotherapy to be tolerable in endometrial cancer.[24][25][26][27] A small (46 patients) RTOG phase II trial of concurrent radiotherapy and cisplatin (two courses), followed by four courses of cisplatin and paclitaxel for high risk or advanced stage endometrial carcinoma has confirmed the feasibility (98% completion rate) and acceptability of the regimen.[25] Surgery consisted of TAH-BSO with or without additional surgical staging. Patients were treated with pelvic RT (45 Gy in 1.8 Gy fractions) plus vaginal brachytherapy. Concurrent chemotherapy with cisplatin 50 mg/m2 was given on days 1 and 22. After RT completion, patients received four additional cycles of cisplatin (50 mg/m2) and paclitaxel (175 mg/m2) at 28-day intervals. Two-year disease-free and overall survival rates were 83% and 90%. The two-year rates of pelvic, regional, and distant recurrence were 2%, 3%, and 17% respectively.

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2.9.1.2.8 Prospective data available about the adjuvant management of uterine papillary serous (UPSC) and clear cell carcinomas (CCC)

A number of small phase II prospective trials in women with UPSC and CCC have been reported. The role of whole abdominal radiotherapy (WART) was evaluated in the GOG 94 trial.[28] Five year progression free survival was relatively higher at 38%. The majority of recurrences were within the radiation field, which led the author to conclude that a combination of chemotherapy and radiotherapy may improve survival outcomes.

The Hoosier Oncology Group reported outcomes of a phase 2 study on 21 patients with stage I and II (pelvic and para-aortic node negative) UPSC and CC. Patients received intraperitoneal radioactive phosphorus ± vaginal brachytherapy. The treatment was extremely well tolerated, with minimal toxicity.[29] The study reported an overall two-year survival rate of 93.3% in the 17 patients who had undergone comprehensive surgical staging. There were two intraperitoneal and two vaginal recurrences (seen in patients who did not receive vaginal brachtherapy).

A prospective clinical trial by Fields and colleagues evaluated pelvic radiation treatment ‘sandwiched’ between six cycles of paclitaxel/platinum chemotherapy in 30 patients with stage I to IV UPSC and reported an overall survival of 75% for patients for stage I and II UPSC and 52% for advanced disease (stages III and IV) at two years.[30] Twelve of the 29 patients available for follow-up (41%) recurred despite this treatment, including 5 of the 16 patients (31%) with stage I disease.

A prospective Canadian cohort study by Lupe et al treated 43 patients with stage III (n=38) and stage IV (n=5) endometrial carcinoma with four cycles of adjuvant carboplatin and paclitaxel chemotherapy followed by pelvic radiotherapy (45Gy) and then another two cycles of chemotherapy.[31] The majority of patients had non-endometrioid histology with serous being the most common (49%). The regimen was feasible to deliver with 81% completing the six cycles of chemotherapy and a manageable rate of acute toxicity. However five patients

(12%) experienced chronic grade 3 radiation toxicities. After a median follow-up of 30 months, 21 patients (49%) had recurred, mostly at distal sites, with the estimated three year disease-free and OS rates being 53% and 68% respectively. The small numbers prevented further analysis of the results by subtype. There have also been other single-arm reports of using this 'sandwich' approach to adjuvant therapy in endometrioid endometrial cancer.[32] However, the only randomised trial reported to date using this approach was negative.[15]

A phase II clinical trial from Australia, enrolled 31 patients with surgically staged Ib-IV UPSC who were treated with four cycles of adjuvant carboplatin (AUC 5) and paclitaxel 175 mg /m2 chemotherapy prior to receiving 50.5 Gy of external beam radiotherapy to the pelvis. The treatment was feasible to deliver and patients reported a stable quality of life with acceptable toxicity. After a median follow-up of 27 months, 13 of the 29 patients with stage 1-3 disease (44.8%) and both of the patients with stage 4 disease developed recurrent disease. The two year survival probabilities were 85.6% for patients with stage 1 or 2 disease and 68.8% for patients with stage 3 disease, and survival rates did not appear superior to a group of historical controls.[33]

Unfortunately, due to the small patient numbers in any one country, there have been no randomised trials that specifically evaluate the use of adjuvant therapy in UPSC and CC. However, this subgroup of patients have been included in some of the randomised trials described earlier on the basis that their disease is also chemo-sensitive and seems to have similar response rates to chemotherapy in the advanced disease setting.[9]

In both the NSGO/EORTC and GOG122 trials, it was not clear that patients with UPSC obtained any benefit from the use of adjuvant chemotherapy. In the NSGO/EORTC trial, patients with serous or clear cell histology made up 37% (n=140) of the trial population. In this subset neither PFS (72% versus 71%), cancer-specific survival (77% versus 78%), nor OS (85% versus 82%) was significantly improved by the addition of the chemotherapy treatment. This finding is similar to what was seen in the GOG122 trial, where the hazard ratio (HR) for death in the 83 women with serous carcinomas was slight above 1.0 in contrast to the HR of 0.48 favoring chemotherapy for the endometrioid cell types.

Although no firm conclusions can be drawn from these results due to small absolute numbers of patients, the trends do not suggest that the addition of adjuvant chemotherapy and/or radiotherapy improves the problem of a high relapse rate for women with UPSC and CC, and it is appropriate that these women are included in the ongoing randomised trials. In addition, it is imperative that alternative molecular targets are identified and pursued in adequately powered prospective trials in this group.

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2.9.1.3 Conclusion

The randomised trials reported to date show no clear overall survival benefit from the use of adjuvant chemotherapy for stage I – III endometrial cancer, with the exception of the GOG122 trial showing that systemic chemotherapy is superior to the use of a sub-optimal radiotherapy regimen. Hence, the value of adjuvant chemotherapy in the management of high-risk endometrial cancer remains uncertain and there is no group of patients with completely resected disease for whom a benefit is clearly demonstrated. Those with stage IV or gross residual disease after surgery do appear to benefit from chemotherapy.

It is likely that some combination of chemotherapy and radiotherapy will be needed to obtain a benefit in earlier stage patients. However, the best type of combination remains to be determined and much more attention needs to be given to the impact of treatment on patient quality of life. Given that many of the trials reported to date are significantly underpowered, with improvements in PFS being seen in some of the more recent studies, the ongoing appropriately powered adjuvant studies being run by the GOG and Gynecologic Cancer Intergroup need to be supported to reach their accrual targets.

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2.9.2 Evidence summary and recommendations

Evidence summary	Level	References
The use of adjuvant chemotherapy alone is not superior to the use of adjuvant pelvic radiotherapy alone in women with stage I - III cancers that have been completely resected with no residual macroscopic disease.	II	[12], [13]
The use of adjuvant chemotherapy plus radiotherapy may improve disease-free and cancer-specific survival compared to the use of adjuvant radiotherapy alone in women with completely resected high-risk stage I-III disease. The benefit is predominantly seen in endometrioid histology. This form of treatment has not been proven to improve overall survival and the impact on quality of life is unknown.	II	[15], [16]

Evidence-based recommendation	Grade
Patients with completely resected stage I-III high-risk disease can be counselled that the use of adjuvant chemotherapy in addition to radiotherapy may improve progression-free survival rates compared to the use of adjuvant radiotherapy alone, particularly if their histology is endometrioid. There is no evidence that overall survival is improved. These patients should be encouraged to consider enrolment into clinical trials addressing this question.	**B**

Evidence summary	Level	References
Some retrospective series suggest that a combination of chemotherapy and radiotherapy may produce better outcomes than radiotherapy alone or no adjuvant treatment in women with UPSC or clear cell carcinomas.	III-3	[34], [35], [36], [37], [38], [39], [40], [41]
Adjuvant chemotherapy and radiotherapy has been safely given in prospective single-arm studies, although recurrence rates remain high (up to 18%).	IV	[29], [30], [31], [33]

Evidence summary	Level	References
Subset analyses of randomised trials show no evidence of improved survival from the use of adjuvant chemotherapy in women with UPSC or clear cell carcinomas.	III-3	[11], [16]

Evidence-based recommendation	Grade
Patients with uterine papillary serous cancer (UPSC) or clear cell (CC) uterine cancer should be counselled that there is only low level evidence that adjuvant chemotherapy may have any impact on survival.	**D**

Evidence summary	Level	References
The optimal sequence of sequential adjuvant chemotherapy and radiotherapy is unknown. Adjuvant chemotherapy can be safely given before or after radiotherapy. In the trial suggesting most benefit from sequential treatment, the majority of patients received chemotherapy after radiotherapy. The most effective and reasonably-tolerated chemotherapy for advanced endometrial cancer appears to be a combination of cisplatin and doxorubicin, or carboplatin and paclitaxel.	II	[15], [16]

Evidence-based recommendation	Grade
Patients treated with sequential adjuvant chemotherapy and radiotherapy may receive the full course of chemotherapy either before or after radiotherapy, or given as part of a sandwich regimen. Acceptable chemotherapy regimens include cisplatin and doxorubicin or carboplatin and paclitaxel.	**C**

Evidence summary	Level	References
The use of chemotherapy alone may improve overall survival compared to the use of radiotherapy alone in women with stage IV disease or stage III disease with residual tumour present at the completion of surgery. The rates of pelvic relapse are high (up to 18%) if adjuvant chemotherapy alone is used.	II	[11]

Evidence-based recommendation	Grade
The use of chemotherapy should be considered for patients with stage IV disease or those with stage III disease plus residual disease at the completion of surgery. Pelvic radiotherapy should also be considered to reduce the risk of pelvic relapse, except perhaps in patients with widespread distant disease.	**B**

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2.9.5 Supporting material

- Initial literature search

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2.10 Guideline development

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- 1.3 Structure the research questions
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- 1.6 Critically appraise the literature
- 1.7 Formulate and grade recommendations
- 1.8 Write the topic content
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- 1.10 Public consultation

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2.10.1 Guideline development process

2.10.1.1 Introduction

Cancer Council Australia (CCA) was commissioned by Cancer Australia (CA) to develop clinical practice guidelines for the treatment and management of endometrial cancer.

The guidelines were developed by a multidisciplinary working group (*see Endometrial Cancer Guidelines Working party members*). Topic leaders from the Working Party membership were designated to address topics in their areas of expertise, with other Working Group members contributing as co-authors.

The guideline development process, conducting the literature searches, appraising the literature and formulating and grading recommendations, followed the NHMRC guideline development process. These guidelines have been developed based on current available evidence. They will be reviewed in the next six months and then as appropriate as new evidence emerges

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2.10.1.2 Steps in preparing clinical practice guidelines

A clear strategy was developed and each topic author followed the appropriate steps in preparing their guideline sections. The Working Party developed clinical questions and topic groups were assigned to review and synthesise the relevant literature and to formulate evidence-based recommendations. The search strategy and literature search was conducted by the Project Officer, who distributed the search results to the Working Party authors.

The strategic steps followed are outlined below:

1. Structure the research questions
2. Develop a search strategy
3. Search the literature
4. Critically appraise the literature
5. Formulate and grade recommendations

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2.10.1.3 Structure the research questions

The Working Party discussed the most important aspects of treatment for women with apparent early stage endometrial cancer and developed clinically focussed key questions. These questions were approved at the Working Party meeting on 27 September 2010.

The clinical questions asked for the **low and high risk apparent early stage disease**, are as follows:

Multidisciplinary care

1. Is there benefit for multidisciplinary care of women with low and high-risk apparent early stage endometrial cancer?

Pre-operative

2. What is the role of preoperative imaging for low and high risk apparent early stage endometrial cancer?

3. Is there a benefit to a histopathological review of currettings or biopsy prior to treatment in low and high risk apparent early stage endometrial cancer?

Surgery

4. What is the evidence based surgical approach for hysterectomy in low and high risk apparent early stage endometrial cancer?

5. What is the evidence based surgical approach for bilateral salpingo–oophorectomy in premenopausal women with low and high risk apparent early stage endometrial cancer?

6. What is the evidence based surgical approach for lymphadenectomy in low and high risk apparent early stage endometrial cancer?

7. What is the role of intra-operative assessment of the uterus in low and high risk apparent early stage endometrial cancer?

Adjuvant Therapy

8. After hysterectomy, what is the role of radiotherapy (external beam, brachytherapy) in the management of early stage high risk endometrial cancer?

9. After hysterectomy, what is the role of chemotherapy (concurrent/concomitant, sequential, sandwich, chemoradiation) in the management of early stage high risk endometrial cancer?

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2.10.1.4 Develop a search strategy

Appropriate search strategies were constructed for each clinical question. MeSH terms were agreed by the Working Party members and where expanded by the Project Officer after conducting pilot searches and searching the MeSH vocabulary. MeSH index terms were translated to Emtree terms for the Embase database to ensure that appropriate index terms unique to each database were used. When there was no appropriate MeSH or Emtree index term available a combination of free text words were used in order to capture the relevant data.

The following exclusion criteria was applied: studies published pre 1995, languages other than English, surgical stage III or IV, advanced, recurrent, metastatic or disseminated endometrial cancer and the following study designs: nonsystematic reviews, case series, case reports, animal, in vitro and laboratory studies and communication such as letters to the editor and journal commentary. The search strategy was approved by the Chair of the Working Party.

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2.10.1.5 Search the literature

A range of medical databases, guideline clearinghouses and clinical trial portals were searched. These included The Cochrane Library, PubMed, Embase, PsycINFO, CINAHL, Scopus, Informit, Trip Database, the National Guideline Clearinghouse, WHO International Clinical Trials Search Portal, the metaRegister of Controlled Trials, the National Institute of Health Registry and the IFPMA Clinical Trials Portal. Search results were screened for relevance by the Project Officer and relevant literature was collated, the full text articles obtained and sent to Working Party topic authors to critically appraise, synthesise and use as the evidence base for their topic questions.

To view the complete search yield and more detailed information about the literature search such as inclusion and exclusion criteria, please go to each clinical question page. The documentation can be found under the heading 'Supporting material'.

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2.10.1.6 Critically appraise the literature

Relevant articles selected from the literature search were reviewed by the clinical question authors and each article was critically appraised with respect to level of evidence, quality of the evidence, size of the effect and clinical importance and relevance. Level of evidence was assigned according to the following criteria adapted from the NHMRC Evidence Hierarchy:

Level	Intervention	Diagnosis	Prognosis	Aetiology	Screening
I	A systematic review of level II studies	A systematic review of level II studies	A systematic review of level II studies	A systematic review of level II studies	A systematic review of level II studies
II	A randomised controlled trial	A study of test accuracy with: an independent, blinded comparison with a valid reference standard, among consecutive patients with a defined clinical presentation	A prospective cohort study	A prospective cohort study	A randomised controlled trial
III-1	A pseudo-randomised controlled trial (i. e. alternate allocation or some other method)	A study of test accuracy with: an independent, blinded comparison with a valid reference standard, among non-consecutive patients with a defined clinical presentation	All or none	All or none	A pseudo-randomised controlled trial (i. e. alternate allocation or some other method)
III-2	A comparative study with concurrent controls: ■ Non-randomised, experimental trial ■ Cohort study ■ Case-control study ■ Interrupted time series with a control group	A comparison with reference standard that does not meet the criteria required for Level II and III-1 evidence	Analysis of prognostic factors amongst untreated control patients in a randomised controlled trial	A retrospective cohort study	A comparative study with concurrent controls: ■ Non-randomised, experimental trial ■ Cohort study ■ Case-control study

Level	Intervention	Diagnosis	Prognosis	Aetiology	Screening
III-3	A comparative study without concurrent controls: ■ Historical control study ■ Two or more single arm study ■ Interrupted time series without a parallel control group	Diagnostic case-control study	A retrospective cohort study	A case-control study	A comparative study without concurrent controls: ■ Historical control study ■ Two or more single arm study
IV	Case series with either post-test or pre-test/post-test outcomes	Study of diagnostic yield (no reference standard)	Case series, or cohort study of patients at different stages of disease	A cross-sectional study	Case series

Source: National Health and Medical Research Council. NHMRC levels of evidence and grades for recommendations for developers of guidelines. Canberra: NHMRC; 2009.[1] (https://www.nhmrc.gov.au/_files_nhmrc/file/guidelines/developers/nhmrc_levels_grades_evidence_120423.pdf)

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2.10.1.7 Formulate and grade recommendations

The body of literature was assessed by each topic author and recommendation grades were assigned using the following criteria adapted from the NHMRC body of evidence matrix:

Component of Recommendation	Recommendation Grade			
	A Excellent	**B Good**	**C Satisfactory**	**D Poor**
		one or two level II studies with low risk of bias or SR/multiple		

Component of Recommendation	Recommendation Grade			
	A Excellent	**B Good**	**C Satisfactory**	**D Poor**
Volume of evidence	several level I or II studies with low risk of bias	level III studies with low risk of bias	level III studies with low risk of bias, or level I or II studies with moderate risk of bias	level IV studies, or level I to III studies with high risk of bias
Consistency	all studies consistent	most studies consistent and inconsistency may be explained	some inconsistency reflecting genuine uncertainty around clinical question	evidence is inconsistent
Clinical impact	very large	Substantial	moderate	slight or restricted
Generalisability	population/s studied in body of evidence are the same as the target population for the guideline	population/s studied in the body of evidence are similar to the target population for the guideline	population/s studied in body of evidence different to target population but it is clinically sensible to for guideline to apply this evidence to target population	population/s studied in body of evidence different to target population and hard to judge whether it is sensible to generalise to target population
Applicability	directly applicable to Australian healthcare context	applicable to Australian healthcare context with few caveats	probably applicable to Australian healthcare context with some caveats	not applicable to Australian healthcare context

Source: National Health and Medical Research Council. NHMRC levels of evidence and grades for recommendations for developers of guidelines. Canberra: NHMRC; 2009.[1] (https://www.nhmrc.gov.au/_files_nhmrc/file/guidelines/developers/nhmrc_levels_grades_evidence_120423.pdf)

Recommendation grades are indicated below:

Grade of recommendation	Description
A	Body of evidence can be trusted to guide practice
B	Body of evidence can be trusted to guide practice in most situations
C	Body of evidence provides some support for recommendation(s) but care should be taken in its application
D	Body of evidence is weak and recommendation must be applied with caution

Grade of recommendation	Description
PP (practice point)	Where no good-quality evidence is available but there is consensus among Guideline committee members, consensus-based guidance points are given, these are called "Practice points"

Adapted from: National Health and Medical Research Council. NHMRC levels of evidence and grades for recommendations for developers of guidelines. Canberra: NHMRC; 2009.[1] (https://www.nhmrc.gov.au/_files_nhmrc/file/guidelines/developers/nhmrc_levels_grades_evidence_120423.pdf)

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2.10.1.8 Write the topic content

Topic authors were asked to write the content for their guideline topic questions using the following format:

- background
- review of the evidence
- evidence summary with levels of evidence and numbered references
- recommendation(s) and corresponding grade(s)
- references

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2.10.1.9 Review of the topic content

The body of evidence and recommendations for each topic question were reviewed by the Guidelines Working Party and final recommendations agreed to, based on the evidence.

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2.10.1.10 Public consultation

A complete draft of the guidelines was sent out for public consultation to all interested parties in Australia for the period from 4 July to 4 August 2011. The consultation process involved soliciting public review of the draft guidelines through posting onto the Cancer Council Australia online Wiki platform and alerting professional societies and groups and sponsors via link to the site.

All feedback on the draft received during the consultation period in Australia was reviewed by the Guidelines Working Party topic authors. Subsequent changes to the draft were agreed by consensus, based on consideration of the evidence.

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2.10.2 References

<references>

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Clinical question	Question authors and contributors
Multidisciplinary care	
Is there benefit for multidisciplinary care of women with low and high-risk apparent early stage endometrial cancer?	Ai Ling Tan - Gynaecological Oncologist Auckland, New Zealand Jane Francis - Manager, Gynaecological Cancers, Cancer Australia
Pre-operative	
What is the role of preoperative imaging for low and high risk apparent early stage endometrial cancer?	Ian Hammond - Gynaecological Oncologist, WA Stuart Salfinger - Gynaecological Oncologist WA Elizabeth Dillon – Diagnostic Radiologist, WA
Is there a benefit to a histopathological review of currettings or biopsy prior to treatment in low and high risk apparent early stage endometrial cancer?	Russell Hogg - Gynaecological Oncologist, NSW
Surgery	
What is the evidence based surgical approach for hysterectomy in low and high risk apparent early stage endometrial cancer?	Andreas Obermair - Gynaecological Oncologist QLD Kym Reid - Gynaecological Oncology Fellow, QLD

Clinical question	Question authors and contributors
Multidisciplinary care	
What is the evidence based surgical approach for bilateral salpingo–oophorectomy in premenopausal women with low and high risk apparent early stage endometrial cancer?	Margaret Davy - Gynaecological Oncologist, SA Alison Brand - Gynaecological Oncologist, NSW
What is the evidence based surgical approach for lymphadenectomy in low and high risk apparent early stage endometrial cancer?	Selvan Pather - Gynaecological Oncologist NSW Marcelo Nascimento - Gynaecological Oncologist, QLD
What is the role of intra-operative assessment of the uterus in low and high risk apparent early stage endometrial cancer?	Colin Stewart - Histopathologist, WA Alison Brand - Gynaecological Oncologist, NSW
Adjuvant Therapy	
After hysterectomy, what is the role of radiotherapy (external beam, brachytherapy) in the management of early stage high risk endometrial cancer?	Robyn Cheuk – Radiation Oncologist, QLD Olivia Bigault – Radiation Oncology Fellow, QLD
After hysterectomy, what is the role of chemotherapy (concurrent/concomitant, sequential, sandwich, chemoradiation) in the management of early stage high risk endometrial cancer?	Andrew Dean – Medical Oncologist, WA Linda Mileshkin- Medical Oncologist, VIC

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2.12 Conflict of interest

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2.12.1 Conflict of interest register and management

Working Party Members were asked to declare in writing, any interests relevant to the guideline development, prior to commencement. Members were asked to update their information if they became aware of any changes to their interests. All declarations were added to a register of interests as listed below.

If Working Party Members were identified as having a significant real or perceived conflict of interest, the Chair could decide that the member either leave the discussion whilst the specific area they were conflicted in was discussed or the member could remain present but not participate in the discussion, or decision making on the specific area where they were conflicted. There were no instances where this occurred during the development of this guideline.

The guidelines have now entered the updating phase. Guideline working party members are responsible to update their conflict of interest statements if a new interest arises. The members will receive a formal reminder to review their statements and ensure it is up-to-date prior to the yearly meetings that will be scheduled to review all updates.

2.12.1.1 Conflict of interest register

2.12.1.1.1 Working party members

Author	Conflict of interest declaration
Dr Alison Brand (Chair) Gynaecological Oncologist – Westmead Hospital, Sydney NSW	No conflict of interest to declare
Professor Ian Hammond (Deputy Chair) Gynaecological Oncologist, Cancer Australia Advisory Group/ King Edward Memorial Hospital, Perth WA	No conflict of interest to declare
Dr Robyn Cheuk	

Author	Conflict of interest declaration
Radiation Oncologist, Cancer Australia Advisory Group/ Royal Brisbane and Womens Hospital, Brisbane QLD	No conflict of interest to declare
Kathryn Crisell Gynaecological cancer consumer, Adelaide SA	No conflict of interest to declare
Assoc Professor Margaret Davy Gynaecological Oncologist, Cancer Australia Advisory Group/ Royal Adelaide Hospital, Adelaide SA	Has been a member of the GSK Advisory Board for Cervarix and also given lectures sponsored by GSK and CSL
Dr Andrew Dean Medical Oncologist, St John of God Hospital, Perth WA	Has been on an Advisory Board for Specialised Therapeutics Australia and received an honorarium from them
Dr Louise Farrell Gynaecologist, King Edward Memorial Hospital, Perth WA	Has received sponsorship to attend meetings from GSK, MSD and CSL. Has received a grant from GSK to run a survey of Gynaecologists' attitude to HPV vaccines. Is an investigator in both CSL and GSK HPV vaccine trials
Jane Francis Manager, Gynaecological Cancers, Cancer Australia	No conflict of interest to declare
Clinical Associate Professor Russell Hogg Gynaecological Oncologist, Westmead Hospital, Sydney NSW	No conflict of interest to declare
Lesley McQuire Gynaecological cancer consumer, Sydney NSW	No conflict of interest to declare
Dr Selvan Pather Gynaecological Oncologist, Royal Prince Alfred Hospital, Sydney NSW	No conflict of interest to declare

Author	Conflict of interest declaration
Dr Frances Quirk Sexologist, Townsville QLD	No conflict of interest to declare
Dr Felicity Rea General Practitioner, Toowoomba QLD	No conflict of interest to declare
Dr Colin Stewart Histopathologist, WA	No conflict of interest to declare
Ella Curnow Project Officer - Cancer Australia	No conflict of interest to declare
Professor Ian Olver AM (Convenor) CEO - Cancer Council Australia	No conflict of interest to declare
Christine Vuletich Manager - Clinical Guidelines Network, Cancer Council Australia	No conflict of interest to declare
Alice Winter-Irving Project Officer - Clinical Guidelines Network, Cancer Council Australia	No conflict of interest to declare
Jutta von Dincklage Project Manager - Wiki Development, Cancer Council Australia	No conflict of interest to declare

2.12.1.1.2 Contributing authors

Author	Conflict of interest declaration
Dr Linda Mileshkin Medical Oncologist, Peter MacCallum Cancer Centre Melbourne VIC	Australian PI for ANZGOG international PORTEC 3 trial. Hospira is supplying paclitaxel for Australian patients in this trial.
Dr Marcelo C Nascimento	

Author	Conflict of interest declaration
Gynaecological Oncologist, Mater Hospital and Gold Coast Hospital, QLD	No conflict of interest to declare
Professor Andreas ObermairGynaecological Oncologist, Queensland Centre for Gynaecological Cancer, The University of Queensland, Brisbane QLD	Has received sponsorship to attend conferences from Gate Health who market the McCartney tube
Dr Kym Reid Gynaecological Oncology Fellow, Brisbane QLD	No conflict of interest to declare
Dr Colin Stewart Histopathologist, St John of God Pathology, Perth WA	No conflict of interest to declare
Ai Ling Tan Gynaecological Oncologist Auckland, New Zealand	Involved in a trial as an investigator sponsored by GSK Prevalance of HPV16,18 in cervical cancer in NZ women